IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Applicant : Ashraf *et al.*

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Examiner : Carter, Kendra D

Customer No. : 38199

Title : SOLID ORAL FORMULATIONS OF RAPAMYCIN 42-ESTER WITH 3-HYDROXY-2-(HYDROXYMETHYL)-2-METHYLPROPIONIC ACID

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Commissioner for Patents
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March 26, 2008

BRIEF ON APPEAL

Sir:

This Appeal Brief is filed subsequent to the Notice of Appeal filed via Electronic Filing System on January 17, 2008. The appeal is from the Office Action dated October 17, 2007 and made final, which rejected pending claims 1-6 and 10-20. An after-final Response was filed on November 21, 2007, and an Advisory Action reiterating the grounds for rejection was mailed on December 27, 2007.

The fee of $510 for filing this Appeal Brief is supplied herewith. A petition for a one-month extension of time from March 17, 2008 through April 17, 2007 and the $120.00 fee for filing same are also filed herewith.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper, or credit any overpayment, to Howson & Howson Deposit Account No. 08-3040.

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I. Real Party in Interest

The real party in interest is the Applicants' assignee, Wyeth, a Delaware corporation located at 5 Giralda Farms, Madison, NJ 17940.

II. Related Appeals and Interferences

None.

III. Status of Claims

The pending claims are claims 1-6 and 10-20. Claims 1-6 and 10-20 (all pending claims) are rejected and are the subject of this appeal.

Claims 1-6. Rejected.

Claims 7-9. Cancelled.

Claims 10-20. Rejected.

IV. Status of Amendments

No amendments were filed subsequent to final rejection.

V. Summary of Claimed Subject Matter

The claims (1-6 and 20) are directed to a solid pharmaceutical composition[1] for oral administration[2] comprising a granulation[3] comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid[4], a water soluble polymer in an amount of about

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[1] This language is supported, *e.g.*, on page 3, line 17; original claim 1; and throughout the specification.

[2] This language is supported, *e.g.*, on page 1, line 10; original claim 1; and throughout the specification.

[3] This language is supported, *e.g.*, on page 3, lines 9, 17-18, and 27-28; page 7, line 3; page 8, line 13; original claim 1, and throughout the specification.

[4] This language is supported, *e.g.*, on page 3, lines 20 and 28; pages 6-8 (tables); original claim 1, and throughout the specification. Rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid is also known as 'CCI-779'.

1% to about 40% (wt/wt)[5], a surfactant in an amount of about 1% to about 8% (wt/wt)[6], an antioxidant from 0.001% to 3% (wt/wt)[7], and a pH modifying agent[8].

The claims (10-14) are further directed to a rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid oral composition prepared by the process[9] comprising dissolving rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid and from 0.001% to 3% (wt/wt)[10] of an antioxidant in an alcohol[11]; dissolving PVP, a pH modifying agent, and a surfactant in water[12]; combining the aqueous and alcoholic solutions to provide a hydroholic solution[13]; adding the hydroalcoholic solution to a mixer containing one or more intragranular excipients[14]; granulating the mixture[15]; and drying the resulting granulation[16].

The claims (15-19) are also directed to a rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid oral formulation prepared by the process comprising dissolving rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid and from 0.001% to 3% (wt/wt) of an antioxidant in an alcohol; dissolving PVP, a pH modifying

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5 This language is supported, *e.g.*, on page 3, lines 21-22; and throughout the specification.

6 This language is supported, *e.g.*, on page 3, line 23; and throughout the specification.

7 This language is supported, *e.g.*, on page 4, line 8-11; and throughout the specification.

8 This language is supported, *e.g.*, on page 3, line 19; original claim 1; and throughout the specification.

9 This language (all of claims 10-14) is supported, *e.g.*, on page 4, line 30-page 5, line 22; original claim 10; and throughout the specification.

10 This language is supported, *e.g.*, on page 4, lines 8-11; original claim 10; and throughout the specification.

11 This language is supported, *e.g.*, on page 4, lines 30-31; original claim 10; and throughout the specification.

12 This language is supported, *e.g.*, on page 4, lines 31-32; original claim 10; and throughout the specification.

13 This language is supported, *e.g.*, on page 5, lines 2-3; original claim 10; and throughout the specification.

14 *Id.*

15 This language is supported, *e.g.*, on page 5, line 8; original claim 10; and throughout the specification.

16 This language is supported, *e.g.*, on page 5, line 10; original claim 10; and throughout the specification.

agent, and a surfactant in water[17]; adding the aqueous and alcoholic solutions stepwise[18], and in one or more portions each, to a mixer containing one or more intragranular excipients[19]; granulating the mixture[20]; and drying the resulting granulation[21].

VI. Grounds of Rejection to be Reviewed on Appeal

A. Whether claims 1-6 and 10-20 are unpatentable under the provisions of 35 U.S.C. §103(a), as obvious over Azrolan[22] in view of Haeberlin[23] and Madhavi[24].

Provisional Obviousness-Type Double Patenting

B. Whether claims 1, 2-6, and 20 are unpatentable (provisionally) on the ground of non-statutory obviousness-type double patenting over claims 55, 58-61, 65 and 72-73 of copending U.S. Patent Application No. 10/930,487 in view of Azrolan.

C. Whether claims 1, 2-6, and 20 are unpatentable (provisionally) on the ground of non-statutory obviousness-type double patenting over claims 1, 7-8 and 11 of copending U.S. Patent Application No. 11/030,685 in view of Azrolan.

D. Whether claims 1, 2, 4, and 6 are unpatentable (provisionally) on the ground of non-statutory obviousness-type double patenting over claims 12-16 and 19 of copending U.S. Patent Application No. 10/626,943.

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17 This language is supported as indicated in preceding footnotes 9-12, and in original claim 15.

18 This language is supported, *e.g.*, on page 5, lines 18-19; original claim 15; and throughout the specification.

19 This language is supported, *e.g.*, on page 5, lines 17-22; original claim 15; and throughout the specification.

20 This language is supported, *e.g.*, on page 5, line 8; original claim 15; and throughout the specification.

21 This language is supported, *e.g.*, on page 5, line 10; original claim 15; and throughout the specification.

22 US Patent Application Publication No. 2002/0013335.

23 UK Patent Application No. GB 2327611.

24 Madhavi, D.L. and Salunkhe, D.K., Food Antioxidants: Technological, Toxicology, and Health Perspectives, pp. 277-293, Decker, 1996.

VII. Argument

A. The examiner has incorrectly rejected claims 1-6 and 10-20 under 35 U.S.C. §103(a) as obvious over Azrolan[25] in view of Haeberlin[26] and Madhavi[27]. Applicants request reversal of the outstanding rejections for the reasons set forth herein.

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.[28]
>
> . . . Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Ascertaining the differences between the claimed invention and the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. [29]
>
> Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. Id. at 17-18, 148 USPQ at 467. Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. . . [30]
>
> In evaluating claims under 35 U.S.C. §103, the claimed invention must be considered as a whole. The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. The references must be viewed without the benefit of

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25 U.S. Patent Application Publication No. 2002/0013335.

26 U.K. Patent Application No. GB 2327611 ("Haeberlin").

27 Madhavi, D.L. and Salunkhe, D.K., Food Antioxidants: Technological, Toxicology, and Health Perspectives, pp. 277-293, Decker, 1996.

28 35 U.S.C. §103(a).

29 MPEP §2141 II., citing *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966).

30 *Id.*

impermissible hindsight vision afforded by the claimed invention. Reasonable expectation of success is the standard with which obviousness is determined.[31]

Exemplary rationales that may support a conclusion of obviousness [under *KSR Int'l Co. v. Teleflex Inc.*] include:

(A) Combining prior art elements according to known methods to yield predictable results; . . .

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; . . . and

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art teachings to arrive at the claimed invention; . . .[32]

1. *The examiner has erred in combining elements of Haeberlin and Madhavi with Azrolan absent predictable results (Exemplary rationale (A)).*

> ...a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.....it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.[33]

Haeberlin and Madhavi add nothing to Azrolan which would **predictably** yield a solid pharmaceutical composition for oral administration comprising a granulation comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779), a water soluble polymer in an amount of about 1% to about

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31 *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

32 MPEP §2143, *citing* KSR Int'l Co. v. Teleflex Inc., 550 U.S. ___ (2007), 127 S. Ct. 1727. While the examiner has not referenced during prosecution her precise rationale for rejection under 35 U.S.C. §103(a), the remaining 'exemplary rationales' listed in MPEP §2143 were not argued by Applicants to be particularly pertinent to these facts during prosecution.

33 KSR Int'l Co. v. Teleflex Inc., 550 U.S. ___ (2007), 82 USPQ2d 1385 at 1396, 127 S. Ct. 1727 at 1741.

40% (wt/wt), a surfactant in an amount of about 1% to about 8% (wt/wt), an antioxidant from 0.001% to 3% (wt/wt), and a pH modifying agent. Similarly, the oral compositions prepared by the processes of independent claims 10 and 15 could not be considered predictable.

None of these documents recognizes the problem to which the present invention is directed, *i.e.*, providing a highly bioavailable non-micronized CCI-779 formulation that avoids both dissolution and instability problems associated with the formation of the CCI-779 compositions of the prior art by compression.[34] Haeberlin provides for stabilization of macrolides, including rapamycins generally, by formulation with an acid such as malonic acid. Madhavi describes the use of BHA and BHT in the food industry.[35] Azrolan describes methods of treating cardiovascular disease with a rapamycin which may include CCI-779. General information regarding excipients useful in formulations is provided.

In the absence of any recognition of the underlying problem or of the beneficial results of the claimed compositions that address these problems, one of skill in the art could not have combined the 'prior art elements' to yield 'predictable results', absent impermissible hindsight. In sum, the examiner calls for combination of elements from macrolide stabilization (Haeberlin), additives in the food industry (Madhavi), and formulation guidance contained in an application directed to treating cardiovascular disease (Azrolan), without any reason one of skill would combine their elements with a reasonable expectation that they would achieve the success obtained by Applicants. The claimed compositions *overcome* the dissolution and instability problems of the art, which are described in the Application's Background of the Invention.[36]

Nowhere during prosecution has the examiner asserted any 'predictable result' identified within the cited documents. Absent such evidence, the examiner's arguments fail to provide any rationale supporting the present obviousness rejection that couldn't be equally (and improperly) applied to any new composition of elements.

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34 Specification at page 3, lines 10-11.

35 Page 277, second paragraph.

36 *See, e.g.*, Specification at page 2, line 30 - page 3, line 4.

In view of the above, the examiner cannot support a finding of obviousness under 35 U.S.C. §103(a). The rejection of the pending claims should be overturned for these reasons.

2. *The examiner has erred in applying an "obvious to try" standard by combining an extensive number of possible solutions without a reasonable expectation of success (Exemplary rationale (E)).*

The Examiner relies on Haeberlin, Madhavi, and Azrolan to supply all the components of the claimed compositions. Azrolan is relied upon for teaching oral formulations of CCI-779 comprising water soluble polymers (*e.g.*, poylvinylpyrrolidone, PVP), surfactants (*e.g.*, sodium lauryl sulfate), and a preservative to prevent microbial growth.[37] Haeberlin is relied upon to provide carboxylic acids as macrolide (pH) stabilizing agents.[38] Madhavi is relied upon for teaching BHA (among other agents) as an antioxidant used in the food industry.

However, the examiner's only rationale for combining Madhavi with Azrolan is the Applicants' specification. The fact that [antioxidants] "BHA and BHT are extensively used antioxidants that are rapidly absorbed from the gastointestinal tract, metabolized and completely excreted in humans"[39] provides no reason to combine with Azrolan. Further, particularly absent any acknowledgement of the problem which Applicants sought to solve, one skilled in the art could not have had a reasonable expectation of success of arriving at the claimed solutions to the problem based on these documents. Similarly, grouping Haeberlin (macrolide stabilization) with Madhavi (antioxidants in the food industry) is purely based on hindsight reasoning.

While the combination alone fails to meet this obviousness rationale, this weakness is compounded by the absence of any reasonable expectation that one of skill could arrive at the claimed combinations given the specific ranges of components claimed. The examiner attempts to buttress this combination of documents by alleging that the ranges

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37 Office Action mailed October 17, 2007 at pages 5-6.

38 *Id.* at page 6, last paragraph.

39 *Id.* at page 8, last paragraph.

of components would be 'obvious to one skilled in the art' based on the language of *In re Boesch*[40]:

> [d]iscovery of an optimum value of the result effective variable in a known process is ordinarily within the skill in the art.[41]

In re Boesch, however, makes this statement based on very different facts. At issue with respect to the Court's use of the above-quoted language was a "result effective variable", *i.e.*, it was known that lowering of the N_v value in a cobalt-chromium-nickel (Co-Cr-Ni) alloy is desirable in that it reduces the chance for precipitation of embrittling phases.

In re Boesch doesn't address the facts of the present application, namely that rather than one 'value' that can be applied to all Co-Cr-Ni alloys, Applicants claims recite pharmaceutical compositions that overcome dissolution and instability problems, reciting a range in claim 1 for a water soluble polymer, a surfactant, and an antioxidant, as well as an antioxidant value in claims 10 and 15. The examiner can identify no parallel standard 'variables' (similar to N_v) in *In re Boesch* that would render Applicants' work a mere optimization. Further, contrary to the examiner's implications, the effectiveness of the ranges claimed is provided within the tables in the Examples to the Specification. Again, Applicants assert that the examiner's arguments fail to provide any rationale supporting the present obviousness rejection that couldn't be equally (and improperly) applied to *any* new composition of elements.

The documents relied upon by the examiner merely provide an extensive number of *possible* solutions, with no particular combination lending a reasonable expectation of success (absent impermissible hindsight). In view of the above, the examiner cannot support a finding of obviousness under 35 U.S.C. §103(a).

The rejection of the pending claims should be overturned for these reasons.

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40 205 USPQ 215, 219, 617 F.2d. 272, 276 (CCPA 1980).

41 Office Action dated October 17, 2007, at page 8, first paragraph.

3. *The examiner has erred in combining Haeberlin, Madhavi, and Azrolan absent any teaching, suggestion, or motivation to combine in order to arrive at the claimed compositions (Exemplary rationale (G)).*

Azrolan describes methods of treating cardiovascular disease with a rapamycin which may include CCI-779. General information regarding excipients useful in formulations is provided. Haeberlin provides for stabilization of macrolides, including rapamycins generally, by formulation with an acid such as malonic acid. Madhavi describes the use of BHA and BHT in the food industry.

Haeberlin and Madhavi do not add anything to Azrolan which would lead one of skill in the art to the solid CCI-779 compositions presently claimed. None of these documents recognizes the problem to which the present invention is directed, *i.e.*, providing a highly bioavailable non-micronized CCI-779 formulation that avoids both dissolution and instability problems associated with the formation of the CCI-779 compositions of the prior art by compression.

The examiner has not provided any motivation to combine these documents to arrive at the pending claims. Absent the Applicants' recognition of the problem on which this invention focuses, nothing in the cited documents suggests the combination of excipients provided by the present formulation, nor could the advantages thereof be predicted. Further, it is not routine within the art to select components, which may or may not have been identified previously, and then derive a formulation of those components in order to solve an unrecognized problem.

The examiner's assertion that one would combine Azrolan with Madhavi because "BHA and BHT are extensively used antioxidants"[42] fails to supply any actual reason to combine. Similarly, that Haeberlin describes the use of acids to stabilize macrolides does not itself supply any motivation to combine with Azrolan. The examiner has provided no reason to combine these documents, except via hindsight to reject Applicants' claimed compositions.

Even if combined, the determination of what percentage of each component to include in the composition could not be derived from these documents by one

[42] Office Action dated October 17, 2007 at page 8, last paragraph.

of skill in the art. Contrary to the Examiner's position[43], it is the inventive selection of components and amounts of same in order to solve the problems identified by the Applicants that yielded the presently claimed compositions.

The Examiner's arguments thus fail to provide any rationale supporting the present obviousness rejection that couldn't be equally (and improperly) applied to any new composition of elements. Accordingly, for the reasons set forth above, the Examiner is respectfully requested to reconsider and withdraw the rejection under 35 USC 103(a).

The rejection of the pending claims should be overturned for these reasons.

B, C, and D - Provisional Obviousness-Type Double Patenting

> A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s).[44]
>
> Where this issue can be addressed without violating the confidential status of applications (35 U.S.C. 122), the courts have sanctioned the practice of making applicant aware of the potential double patenting problem if one of the applications became a patent by permitting the examiner to make a "provisional" rejection on the ground of double patenting.[45]
>
> The merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to issue.[46]

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43 *Id.* at page 8, first paragraph.

44 MPEP §804.II.B.1.

45 MPEP §804.I.B.

46 *Id.*

KSR v. Teleflex reiterates the rule that "[t]o faciliate review [of an obviousness analysis], this analysis should be made explicit."[47] *KSR* quotes *In re Kahn* as a source for this requirement,

> rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.[48]

B. The examiner has incorrectly provisionally[49] rejected claims 1, 2-6 and 20 on the ground of non-statutory obviousness-type double patenting over claims 55, 58-61, 65 and 72-73 of copending U.S. Patent Application No. 10/930,487 (claims renumbered upon issuance of U.S. Patent No. 7,271,177 - see footnote 44), in view of Azrolan. Applicants request reversal of the outstanding rejections for the reasons set forth herein.

> Claims 27, 30-33, 37 and 44-45 of U.S. Patent No. 7,271,177 read as follows:
>
> 27. A pharmaceutical composition comprising an amorphous form of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid, comprising:
>
> (i) an amorphous form of rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid according to claim 1, (ii) a metal chelator, (iii) a pH adjuster, (iv) a surfactant, (v) at least one filler, (vi) a binder, (vii) a disintegrant, and (viii) a lubricant.
>
> 30. The pharmaceutical composition according to claim 27, wherein said pH adjuster comprises citric acid, ascorbic acid, fumaric acid, or malic acid.
>
> 31. The pharmaceutical composition according to claim 30, wherein said pH adjuster is citric acid.

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47 KSR Int'l Co. v. Teleflex Inc., 550 U.S. ___ (2007), 82 USPQ2d 1385 at 1396. Applicants note that this guidance was provided in the Court's discussion regarding the combination of elements (substitution of one element for another). However, it is applicable to any obviousness rejection, as evidenced by *In re Kahn*, 441 F.3d 977 [78 USPQ2d 1329](CA Fed. 2006).

48 *Id.*, quoting *In re Kahn*, 441 F.3d 977, 988 [78 USPQ2d 1329](CA Fed. 2006).

49 U.S. Patent Application No. 10/930,487 has now issued as U.S. Patent No. 7,271,177 (issued September 18, 2007). Accordingly, the provisional status of this rejection will likely be withdrawn. Claims 55, 58-61, 65 and 72-73 were renumbered upon issuance as claims 27, 30-33, 37 and 44-45, respectively.

32. The pharmaceutical composition according to claim 30, wherein said surfactant is selected from a polysorbate, a sorbitan ester, poloxamer, or sodium lauryl sulfate.

33. The pharmaceutical composition according to claim 32, wherein said surfactant is sodium lauryl sulfate.

37. The pharmaceutical composition according to claim 27, wherein said binder comprises povidone, hydroxypropylmethylcellulose, carboxymethylcellulose, or gelatin.

44. The pharmaceutical composition according to claim 27, wherein said components are dry granulated and compressed into a form suitable for administration to a mammalian subject.

45. The pharmaceutical composition according to claim 27, wherein said components are dry granulated and compressed into a form suitable for administration to a mammalian subject.

The examiner has failed to clearly articulate a rationale for obviousness, separate from hindsight reasoning in view of the pending claims.

The Office Action mailed October 17, 2007 provides the examiner's most recent (and complete) iteration of the rejection.[50] The examiner indicates that the '177 patent ('487 application) claims a composition comprising CCI-779, a water soluble polymer (hydroxypropylmethylcellulose), and a surfactant, *in addition to* the following features: the CCI-779 being in amorphous form, and the presence of a metal chelator, a pH adjuster, at least one filler, a binder, a disintegrant, and a lubricant. The examiner indicates that from this very specific formulation, one of skill in the art would combine formulation information from Azrolan, which is directed to methods of treating cardiovascular disease with a rapamycin (CCI-779 included) to arrive at the claimed compositions. There is no explanation as to how these documents would be combined by one of ordinary skill in the art, nor is there any explanation as to how one of skill in the art would arrive at the percentages of components claimed by Applicants. The examiner's only guidance is conclusory statements of obviousness.[51]

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50 Pages 10-13.

51 Office Action mailed October 17, 2007 at page 13, lines 4 and 5.

In summary, the examiner's rejections read as a recital of the claimed formulation of the '177 patent, a recital of teachings in Azrolan, and then a bare assertion that "[o]ne of ordinary skill in the art would find it obvious [to prepare the claimed compositions]."[52] Thus, the examiner has failed to articulate her reasoning for this obviousness-type double patenting rejection.

The documents relied upon by the examiner may not be combined to render the pending claims obvious.

In sum, the '177 patent contains claims drawn to narrow formulations containing amorphous CCI-779. Azrolan, with which the '177 patent is combined, describes methods of treating cardiovascular disease with a rapamycin which may include CCI-779, and includes general information regarding excipients useful in formulations is provided. One of skill in the art would not combine Azrolan with the '177 patent to arrive at the pending claims, by any rationale, including those set forth above[53], *i.e.*, (i) combining prior art elements according to known methods to yield predictable results, (ii) "obvious to try", or (iii) a teaching, suggestion, or motivation in the prior art.

The examiner appears to argue in the Office Actions that one of skill in the art would modify the specific formulation claimed in the '177 patent ('487 application) by removing a number of required components[54] in view of Azrolan, which is focused on the treatment of cardiovascular disease. While the examiner considers this conclusion is 'obvious', Applicants assert that one of skill in the art would never reach this conclusion, absent impermissible hindsight reasoning. The '177 patent has a priority date of September 3, 2003. Thus, there is no motivation for one to modify these formulations using the teachings of the earlier-published Azrolan application (published January 21, 2002) in order to arrive at the pending claims.

An 'obvious to try' justification is inappropriate given the present facts, given the examiner fails to provide any rationale supporting this obviousness-type double patenting

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52 *Id.* at page 13, first full paragraph.

53 *See* Section VII.A. (35 U.S.C. §103(a)), *supra*, at page 6.

54 The CCI-779 being in amorphous form, and the presence of a metal chelator, a pH adjuster, at least one filler, a binder, a disintegrant, and a lubricant.

rejection that couldn't be equally (and improperly) applied to *any* new composition of elements. Similarly, combining known elements to achieve a predictable result is an inapplicable justification, given that there are an extensive number of possible compositions. Further, one of skill in the art would not have a reasonable expectation of success in identifying the claimed compositions absent recognition of the problem to be solved by the Applicants - a highly bioavailable non-micronized CCI-779 formulation that overcomes the dissolution and instability problem.[55]

In view of the above, the examiner cannot support the obviousness-type double patenting rejection based on the claims of U.S. Patent No. 7,271,177 in view of Azrolan. The rejection of claims 1, 2-6 and 20 should be overturned for these reasons.

C. The examiner has incorrectly provisionally rejected claims 1, 2-6 and 20 on the ground of non-statutory obviousness-type double patenting over claims 1, 7-8 and 11 and 72-73 of copending U.S. Patent Application No. 11/030,685 in view of Azrolan. Applicants request reversal of the outstanding rejections for the reasons set forth herein.

Claims 1, 7-8 and 11 of U.S. Patent Application No. 11/030,685 read as follows:

> 1. A pharmaceutical composition comprising micronized CCI-779.
>
> 7. The pharmaceutical composition according to claim 1, further comprising:
> about 5% w/w to about 6/5% w/w surfactant;
> about 80% w/w to about 85% w/w filler/binder;
> about 4% w/w to about 6% w/w disintegrant.
>
> 8. The pharmaceutical composition according to claim 7, wherein the surfactant is sodium lauryl sulfate.
>
> 11. The pharmaceutical composition according to claim 1, further comprising one or more antioxidants, a chelating agent and/or a pH modifier.

The examiner has failed to clearly articulate a rationale for obviousness, separate from hindsight reasoning in view of the pending claims.

[55] Specification at page 3, lines 10-11.

The Office Action mailed October 17, 2007 provides the examiner's most recent (and complete) iteration of the rejection.[56] The examiner indicates that the '685 application claims a composition comprising micronized CCI-779 (claim 1); a surfactant, a filler/binder, a disintegrant (claim 7); and one or more antioxidants, a chelating agent, and/or a pH modifier (claim 11). The examiner combines Azrolan to teach a composition of CCI-779 comprising polyvinylpyrrolidone.[57]

There is no explanation provided by the examiner as to how one of skill in the art would arrive at the claimed compositions. Further, there is no explanation as to one of skill in the art would arrive at the percentages of components claimed by Applicants, aside from the conclusory statement that these ranges are "obvious to one skilled in the art to obtain."[58] Thus, the examiner has failed to articulate her reasoning for this obviousness-type double patenting rejection.

The documents relied upon by the examiner may not be combined to render the pending claims obvious.

> [i]t is improper to combine references where the references teach away from their combination.[59]

In sum, the '685 application contains claims drawn to compositions comprising micronized CCI-779, which may also include a surfactant, filler/binder, disintegrant, and one or more antioxidants, a chelating agent, and/or a pH modifier. Azrolan, with which the '685 application is combined, is directed to methods of treating cardiovascular disease with a rapamycin which may include CCI-779. One of skill in the art would not arrive at the pending claims based on the '685 application, with or without combination with Azrolan.

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56 Pages 13-15.

57 *See* pending (Applicants') claim 20.

58 Office Action mailed October 17, 2007 at page 15, last two lines.

59 MPEP §2145 X.D.2., citing *In re Grasselli*, 713 F.2d. 731, 743; 218 USPQ 769, 779 (Fed. Cir. 1983)("The claimed catalyst which contained both iron and an alkali metal was not suggested by the combination of a reference which taught the interchangeability of antimony and an alkali metal with the same beneficial result, combined with a reference expressly excluding antimonry from, and adding iron to, a catalyst.")

The examiner asserts at page 14, last paragraph of the October 17, 2007 Office Action that

> [o]ne having ordinary skill in the art would find it obvious to formulate a pharmaceutical composition comprising a water soluble polymer and a composition comprising a granulation according to 11/030,685 because hydroxypropylmethylcellulose (see claim 26) is a water soluble polymer and the composition is in granular form due to formation of a tablet (see claim 27).

However, having read the specification of the '685 application, one of skill in the art would be *lead away from* the claimed compositions comprising a granulation.

The specification of the '685 application teaches that one of its aims is in improvement of the formulations presently claimed, namely in seeking a simpler manufacturing process that provides a more thermodynamically stable CCI-779. The specification indicates that

> [a] CCI-779 formulation was developed that employed a wet granulation manufacturing process. US Published Patent Application, Publication No. US-2004-0077677-A1 [the publication of the present application]. This process involved preparation of a hydroalcoholic granulation solution of CCI-779. Further, although the resulting tablets were stable and bioavailable, the **preparation of the hydroalcoholic solution was very tedious**. Further, CCI-779 was **thermodynamically unstable, precipitating within one day after its preparation**, requiring it to be used immediately after its preparation.[60]

Having read the above passage, one of skill in the art would not, alone or with another document, apply the '685 application to arrive at the pending claims. The examiner is also incorrect within her brief explanation for her finding of obviousness.[61] Contrary to her assertions, claim 26 of the '685 application refers to hydroxypropylmethylcellose as part of the composition, where it is actually within a 'seal coating'. Further, claim 27's reference to a tablet does not imply that the composition is in granular form. To the contrary, the only granulation utilized was as a control.[62]

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60 Specification of U.S. Patent Application No. 11/030,685, page 2, lines 8-14 (emphasis added).

61 Office Action mailed October 17, 2007 at page 14, last paragraph (quoted above).

62 Specification of U.S. Patent Application No. 11/030,685, page 16, lines 1-2.

The '685 application teaches away from the pending claims, and thus may not (alone or in combination) form the basis for an obviousness rejection. In view of the above, the examiner cannot support the obviousness-type double patenting rejection based on the claims of U.S. Patent Application No. 11/030,685 in view of Azrolan. The rejection of claims 1, 2-6 and 20 should be overturned for these reasons.

D. The examiner has incorrectly provisionally rejected claims 1, 2, 4 and 6 on the ground of non-statutory obviousness-type double patenting over claims 12-16 and 19 of copending U.S. Patent Application No. 10/626,943. Applicants request reversal of the outstanding rejections for the reasons set forth herein.

Claims 12-16 and 19 of U.S. Patent Application No. 10/626,943 read as follows:

> 12. A parenteral formulation which comprises CCI-779, an alcoholic solvent, an antioxidant, a diluent solvent, and a surfactant.
>
> 13. The formulation according to claim 12, wherein the alcoholic solvent is ethanol, propylene glycol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, or polyethylene glycol 1000.
>
> 14. The formulation according to claim 12, wherein the antioxidant is citric acid, glycine, d,1-a-tocopherol, BHA, BHT, monothoglycerol, ascorbic acid, or propyl gallate.
>
> 15. The formulation according to claim 12, wherein the diluent solvent is water, ethanol, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 1000, or propylene glycol.
>
> 16. The formulation according to claim 12, wherein the surfactant is polysorbate 20, polysorbate 80, a bile acid, lecithin, an ethoxylated vegetable oil, vitamin E, or polyoxyethylene-polyoxyproylene block copolymers.
>
> 19. The formulation according to claim 12, wherein the formulation comprises a concentration of antioxidant from about 0.0005 to 0.5% w/v.

The examiner's justification for the obviousness-type double patenting rejection is that

> [o]ne having ordinary skill in the art would find it obvious to formulate a pharmaceutical composition comprising a solid granulation because **it is a species of the genus parenteral formulation** (see claim 12). In other words, **a parenteral formulation can be in a solid** granulation and since there are no reasons why the solid form gives results that produce unexpected results, then the solid granulation form is obvious to one skilled in the art to obtain.[63]

The examiner's obviousness rejection is based on errant assumptions.

One of skill in the art of pharmaceutical compositions readily understands that the term "parenteral" is defined as

> not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc.[64]

The term "alimentary" meaning

> pertaining to food or nutritive material, or to the organs of digestion.[65]

Thus, the '943 application's claims to *parenteral* formulations would not lead one of ordinary skill in the art to prepare *solid* pharmaceutical compositions for *oral* administration. The very definition of parenteral *excludes* oral administration. Further, preparation of a granulation would not be considered obvious in view of formulations for parenteral administration.

Given the examiner's only stated rationale for the provisional obviousness-type double patenting rejection requires that a solid granulation be a species of the genus of parenteral formulations, the examiner cannot support the obviousness-type double patenting rejection.

The rejection of claims 1, 2, 4, and 6 should be overturned for these reasons.

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63 Office Action mailed October 17, 2007, at page 17, last paragraph, through the top of page 18 (emphasis added).

64 *See, e.g.*, Dorland's Illustrated Medical Dictionary, Twenty-sixth Edition, at pg. 970 (1985).

65 *Id.* at page 47.

For the reasons provided herein, the examiner has improperly rejected the claims which are the subject of the present appeal under 35 U.S.C. §103(a) and the doctrine of obviousness-type double patenting. Accordingly, reversal of the examiner's rejection of the claims under appeal (claims 1-6 and 10-20) is requested.

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VIII. Claims Appendix

1 (Previously presented): A solid pharmaceutical composition for oral administration comprising a granulation, said granulation comprising

rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid,

a water soluble polymer in an amount of about 1 % to about 40% (wt/wt),

a surfactant in an amount of about 1 % to about 8% (wt/wt), an antioxidant from 0.001% to 3% (wt/wt), and a pH modifying agent.

2 (Original): The composition of claim 1, wherein the water soluble polymer is PVP, hydroxypropylmethylcellulose, polyethylene glycol, or cyclodextrin or mixtures thereof.

3 (Original): The composition of claim 2, wherein the water soluble polymer is PVP.

4 (Previously presented): The composition of claim 1, wherein the surfactant is polysorbate 80, sodium lauryl sulfate, sodium dodecyl sulfate, a salt of a bile acid, an ethoxylated vegetable oil, a polyoxyethylene-polyoxypropylene block copolymer, or a poloxamer.

5 (Original): The composition of claim 4, wherein the surfactant is sodium lauryl sulfate or sodium dodecyl sulfate.

6 (Previously presented): The pharmaceutical composition of claim 1, wherein the pH modifying agent is sodium citrate, citric acid, or dilute hydrochloric acid.

Claims 7 - 9 (Cancelled).

10 (Previously presented): A rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid oral composition prepared by the process comprising:

(a) dissolving rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid and from 0.001% to 3% (wt/wt) of an antioxidant in an alcohol;

(b) dissolving PVP, a pH modifying agent, and a surfactant in water;

(c) combining the aqueous and alcoholic solutions to provide a hydroholic solution;

(d) adding the hydroalcoholic solution to a mixer containing one or more intragranular excipients;

(e) granulating the mixture; and

(f) drying the resulting granulation.

11 (Original): The composition of claim 10, wherein the pH modifying agent is selected from the group consisting of citric acid, sodium citrate, hydrochloric acid and mixtures thereof.

12 (Original): The composition of claim 11, wherein the alcohol is ethanol.

13 (Original): The composition of claim 12, wherein the antioxidant is butylated hydroxyanisole and butylated hydroxytoluene.

14 (Original): The composition of claim 13, wherein the surfactant is sodium lauryl sulfate.

15 (Previously presented): A rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid oral formulation prepared by the process comprising:

(a) dissolving rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid and from 0.001% to 3% (wt/wt) of an antioxidant in an alcohol;

(b) dissolving PVP, a pH modifying agent, and a surfactant in water;

(c) adding the aqueous and alcoholic solutions stepwise, and in one or more portions each, to a mixer containing one or more intragranular excipients;

(d) granulating the mixture; and

(e) drying the resulting granulation.

16 (Original): The composition of claim 15, wherein the pH modifying agent is selected from the group consisting of citric acid, sodium citrate, hydrochloric acid and mixtures thereof.

17 (Original): The composition of claim 16, wherein the alcohol is ethanol.

18 (Original): The composition of claim 17, wherein the antioxidant is butylated hydroxyanisole and butylated hydroxytoluene.

19 (Original): The composition of claim 18, wherein the surfactant is sodium lauryl sulfate.

20 (Previously presented): The pharmaceutical composition according to claim 1, comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid present in an amount of about 1% (wt/wt) to about 5% (wt/wt),

polyvinylpyrrolidone in an amount of about 5% (wt/wt) to about 20% (wt/wt);

a surfactant comprising sodium laurel sulfate in an amount of about 3% to about 5% (wt/wt), and

citric acid.

IX. Evidence Appendix

Page

Non-Patent Literature

I. INSTANCES WHERE DOUBLE PATENTING ISSUE CAN BE RAISED

A double patenting issue may arise between two or more pending applications, or between one or more pending applications and a patent. A double patenting issue may likewise arise in a reexamination proceeding between the patent claims being reexamined and the claims of one or more applications and/or patents. Double patenting does not relate to international applications which have not yet entered the national stage in the United States.

A. Between Issued Patent and One or More Applications

Double patenting may exist between an issued patent and an application filed by the same inventive entity, or by a different inventive entity having a common inventor, and/or by a common assignee/owner. Double patenting may also exist where the inventions claimed in a patent and an application were made as a result of activities undertaken within the scope of a joint research agreement as defined in 35 U.S.C. 103(c)(2) and (3). Since the inventor/patent owner has already secured the issuance of a first patent, the examiner must determine whether the grant of a second patent would give rise to an unjustified extension of the rights granted in the first patent.

B. Between Copending Applications—Provisional Rejections

Occasionally, the examiner becomes aware of two copending applications that were filed by the same inventive entity, or by different inventive entities having a common inventor, and/or by a common assignee, or that claim an invention resulting from activities undertaken within the scope of a joint research agreement as defined in 35 U.S.C. 103(c)(2) and (3), that would raise an issue of double patenting if one of the applications became a patent. Where this issue can be addressed without violating the confidential status of applications (35 U.S.C. 122), the courts have sanctioned the practice of making applicant aware of the potential double patenting problem if one of the applications became a patent by permitting the examiner to make a "provisional" rejection on the ground of double patenting. *In re Mott,* 539 F.2d 1291, 190 USPQ 536 (CCPA 1976); *In re Wetterau,* 356 F.2d 556, 148 USPQ 499 (CCPA 1966). The merits of such a provisional rejection can be addressed by both the applicant and the examiner without waiting for the first patent to issue.

The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.

1. Nonstatutory Double Patenting Rejections

If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer. If the ODP rejection is the only rejection remaining in the later-filed application, while the earlier-filed application is rejectable on other grounds, a terminal disclaimer must be required in the later-filed application before the rejection can be withdrawn.

If "provisional" ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue. If both applications are filed on the same day, the examiner should determine which application claims the base invention and which application claims the improvement (added limitations). The ODP rejection in the base application can be withdrawn without a terminal disclaimer, while the ODP rejection in the improvement application cannot be withdrawn without a terminal disclaimer.

additionally be made in the later-filed application using form paragraph 7.15.01.

If the "same invention" is not being claimed twice, an analysis must be made to determine whether a nonstatutory basis for double patenting exists.

B. Nonstatutory Double Patenting

A rejection based on nonstatutory double patenting is based on a judicially created doctrine grounded in public policy so as to prevent the unjustified or improper timewise extension of the right to exclude granted by a patent. *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re White*, 405 F.2d 904, 160 USPQ 417 (CCPA 1969); *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968); *In re Sarett*, 327 F.2d 1005, 140 USPQ 474 (CCPA 1964).

1. Obviousness-Type

>A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).< In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is — does any claim in the application define an invention that is >anticipated by, or is< merely an obvious variation of >,< an invention claimed in the patent? If the answer is yes, then an "obviousness-type" nonstatutory double patenting rejection may be appropriate. Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the subject matter claimed in a commonly owned patent, or a non-commonly owned patent but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3), when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. See *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 USPQ2d 1869 (Fed. Cir. 2001); *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000).

A double patenting rejection of the obviousness-type>, if not based on an anticipation rationale,< is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, *>the< analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis. These factual inquiries are summarized as follows:

(A) Determine the scope and content of a patent claim relative to a claim in the application at issue;

(B) Determine the differences between the scope and content of the patent claim as determined in (A) and the claim in the application at issue;

(C) Determine the level of ordinary skill in the pertinent art; and

(D) Evaluate any objective indicia of nonobviousness.

The conclusion of obviousness-type double patenting is made in light of these factual determinations.

Any obviousness-type double patenting rejection should make clear:

(A) The differences between the inventions defined by the conflicting claims — a claim in the patent compared to a claim in the application; and

(B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim at issue >is anticipated by, or< would have

nation is obvious." Id. at ___, 82 USPQ2d at 1395-96 (Internal quotations omitted.). The principles underlining these cases are instructive when the question is whether a patent application claiming the combination of elements of prior art would have been obvious. The Supreme Court further stated that:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Id.* at ___, 82 USPQ2d at 1396.

When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id* . at ___, 82 USPQ2d at 1396.

II. The Basic Factual Inquiries of Graham v. John Deere Co.

An invention that would have been obvious to a person of ordinary skill at the time of the invention is not patentable. See 35 U.S.C. 103(a). As reiterated by the Supreme Court in *KSR*, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows:

(A) Ascertaining the differences between the claimed invention and the prior art; and

(B) Ascertaining the differences between the claimed invention and the prior art; and

(C) Resolving the level of ordinary skill in the pertinent art.

Objective evidence relevant to the issue of obviousness must be evaluated by Office personnel. *Id.* at 17-18, 148 USPQ at 467. Such evidence, sometimes referred to as "secondary considerations," may include evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. The evidence may be included in the specification as filed, accompany the application on filing, or be provided in a timely manner at some other point during the prosecution. The weight to be given any objective evidence is made on a case-by-case basis. The mere fact that an applicant has presented evidence does not mean that the evidence is dispositive of the issue of obviousness.

The question of obviousness must be resolved on the basis of these factual determinations. While each case is different and must be decided on its own facts, the *Graham* factors, including secondary considerations when present, are the controlling inquiries in any obviousness analysis. The *Graham* factors were reaffirmed and relied upon by the Supreme Court in its consideration and determination of obviousness in the fact situation presented in *KSR*, 550 U.S. at ___, 82 USPQ2d at 1391 (2007). The Supreme Court has utilized the *Graham* factors in each of its obviousness decisions since *Graham*. See *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 189 USPQ 449, *reh'g denied*, 426 U.S. 955 (1976); *Dann v. Johnston*, 425 U.S. 219, 189 USPQ 257 (1976); and *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 163 USPQ 673 (1969). As stated by the Supreme Court in *KSR*, "While the sequence of these questions might be reordered in any particular case, the [*Graham*] factors continue to define the inquiry that controls."*KSR*, 550 U.S. at ___, 82 USPQ2d at 1391.

Office Personnel As Factfinders

Office personnel fulfill the critical role of factfinder when resolving the *Graham* inquiries. It must be remembered that while the ultimate determination of obviousness is a legal conclusion, the underlying *Graham* inquiries are factual. When making an obviousness rejection, Office personnel must therefore ensure that the written record includes findings of fact concerning the state of the art and the teachings of the references applied. In certain circumstances, it may also be important to include explicit findings as to how a person of ordinary skill would have understood prior art teachings, or what a person of ordinary skill would have known or could have done. Factual findings made by Office personnel are the necessary underpinnings to establish obviousness.

Once the findings of fact are articulated, Office personnel must provide an explanation to support an obviousness rejection under 35 U.S.C. 103. 35 U.S.C.

(2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 (quoting Federal Circuit statement with approval). <

If the examiner determines there is factual support for rejecting the claimed invention under 35 U.S.C. 103, the examiner must then consider any evidence supporting the patentability of the claimed invention, such as any evidence in the specification or any other evidence submitted by the applicant. The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). The legal standard of "a preponderance of evidence" requires the evidence to be more convincing than the evidence which is offered in opposition to it. With regard to rejections under 35 U.S.C. 103, the examiner must provide evidence which as a whole shows that the legal determination sought to be proved (i.e., the reference teachings establish a *prima facie* case of obviousness) is more probable than not.

When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must reconsider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of all the evidence, including the evidence submitted by the examiner and the evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of obviousness was reached, not against the conclusion itself. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990).

See *In re Piasecki*, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984) for a discussion of the proper roles of the examiner's *prima facie* case and applicant's rebuttal evidence in the final determination of obviousness. See MPEP § 706.02(j) for a discussion of the proper contents of a rejection under 35 U.S.C. 103.

2143 >Examples of< Basic Requirements of a *Prima Facie* Case of Obviousness

**>The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham*. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.

EXEMPLARY RATIONALES

Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (Claims were directed to an epoxy resin based printed circuit material. A prior art reference disclosed a polyester-imide resin based printed circuit material, and taught that although epoxy resin based materials have acceptable stability and some degree of flexibility, they are inferior to polyester-imide resin based materials. The court held the claims would have been obvious over the prior art because the reference taught epoxy resin based material was useful for applicant's purpose, applicant did not distinguish the claimed epoxy from the prior art epoxy, and applicant asserted no discovery beyond what was known to the art.).

Furthermore, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

2. References Cannot Be Combined Where Reference Teaches Away from Their Combination

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) (The claimed catalyst which contained both iron and an alkali metal was not suggested by the combination of a reference which taught the interchangeability of antimony and alkali metal with the same beneficial result, combined with a reference expressly excluding antimony from, and adding iron to, a catalyst.).

3. Proceeding Contrary to Accepted Wisdom Is Evidence of Nonobviousness

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) (Applicant's claimed process for sulfonating diphenyl sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures.).

Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966).

XI. FORM PARAGRAPHS

See MPEP § 707.07(f) for form paragraphs 7.37 through 7.38 which may be used where applicant's arguments are not persuasive or are moot.

2146 35 U.S.C. 103(c) [R-3]

35 U.S.C. 103. Conditions of patentability; non-obvious subject matter.

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**>

(c)(1) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

(2) For purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person if —

(A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date the claimed invention was made;

(B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(3) For purposes of paragraph (2), the term "joint research agreement" means a written contract, grant, or cooperative agreement entered into by two or more persons or entities for the performance of experimental, developmental, or research work in the field of the claimed invention.<

**>Effective November 29, 1999, subject matter which was prior art under former 35 U.S.C. 103 via 35 U.S.C. 102(e) was disqualified as prior art against the claimed invention if that subject matter and the claimed invention "were, at the time the invention

321 (1974). While the $10,000 awarded plaintiffs in fees might be considered generous when compared with the amount recovered in damages, the fees do not appear unreasonable considering the amount of work necessitated and performed and the skill employed. See also Key West Hand Print Fabrics, 269 F.Supp. at 615-16, 155 USPQ at 132-133. There was no abuse here.

However, we deny plaintiffs' application for allowance of additional attorneys' fees on appeal. We assume counsel was familiar with the law, having made similar arguments in district court on all the issues raised on appeal. See Monogram Models, 492 F.2d at 1288, 181 USPQ at 429. The appeal was not frivolous. Plaintiffs did not prevail on their cross appeal. Equity considerations lead us to permit the parties to pay their own attorneys' fees in this court. The plaintiffs are entitled to costs.

Affirmed.

Court of Customs and Patent Appeals

In re Boesch and Slaney

No. 79-597

Decided Mar. 13, 1980

PATENTS

1. Patentability — Invention — In general (§51.501)

Patentability — Invention — Specific cases — In general (§51.5091)

Discovery of optimum value of result effective variable in known process is ordinarily within skill of art.

2. Patentability — Composition of matter (§51.30)

Patentability — Evidence of — In general (§51.451)

Patentability — Evidence of — Comparison with allowed claims or patents (§51.457)

Patentability — Invention — In general (§51.501)

Patentability — Invention — Specific cases — In general (§51.5091)

Prima facie case of obviousness may be rebutted where results of optimizing variable, which was known to be result effective, are unexpectedly good; proof of unexpected properties may be in form of direct or indirect comparative testing of claimed compounds and closest prior art.

3. Patentability — Composition of matter (§51.30)

Patentability — Evidence of — In general (§51.451)

Patentability — Evidence of — Comparison with allowed claims or patents (§51.457)

Patentability — Invention — Specific cases — Chemical (§51.5093)

Data that compares four examples of claimed alloys with one example of prior art alloy and is intended to show unexpected results are not commensurate in scope with claims for broad range of elements in case in which weight percent of elements in four examples of claimed alloys vary by relatively minor amounts, for example, entire claimed range of carbon is .18 percent, but tested range is only .02, and claimed cobalt range is 4.8, but test range is only 1.3, and there is no evidence showing whether other alloys encompassed by these broad claims and having elements varying by relatively major amounts also exhibit unexpected results.

4. Patentability — Composition of matter (§51.30)

Patentability — Evidence of — In general (§51.451)

Patentability — Evidence of — Comparison with allowed claims or patents (§51.457)

Patentability — Invention — Specific cases — Chemical (§51.5093)

Test results involving single alloy within broad range claimed are not sufficient to support appellants' allegation of what would, from prior art, be unexpected under circumstances in which essential concept of invention is to maintain average number of electron vacancies at value not exceeding about 2.35, prior art teaches that reduction of Nv value reduces the chances of sigma phase in alloy, appellants allege that alloys meeting their composition and Nv value requirements are free from sigma phase, and appellants tested only one example of low Nv value alloy and found no sigma, which is result consistent with both prior art

teaching and appeallants' allegation that their claimed alloys are totally free from sigma phase; where it is alleged that certain technique for flipping coins would always produce "heads," one would hardly be persuaded by single toss of coin that resulted in showing of "heads."

Particular patents — Nickel Alloys

Boesch and Slaney, Temperature Nickel Based Alloy and Process of Making Same, rejection of claims 1 and 8-15 affirmed.

Appeal from Patent and Trademark Office Board of Appeals.

Application for patent of William J. Boesch and John S. Slaney, Serial No. 587,776, filed June 17, 1975. From decision rejecting claims 1 and 8-15, applicants appeal. Affirmed.

Robert F. Dropkin and Vincent G. Gioia, both of Pittsburgh, Pa., for appellants.

Joseph F. Nakamura (John W. Dewhirst, of counsel) for Commissioner of Patents and Trademarks.

Before Markey, Chief, Judge, Rich, Baldwin, and Miller, Associate, Judges, and Maletz,* Judge.

Miller, Judge.

This is an appeal from a decision of the Patent and Trademark Office ("PTO") Board of Appeals ("board") which sustained the examiner's rejection under 35 USC 103 of appellants' claims[1] 1 and 8-15 in view of Lamb[2] and Pohlman[3] et al. We affirm.

Invention

The invention embraces nickel base alloys consisting essentially of:

Metals	Percentage Ranges
aluminum	4.0 - 4.7
boron	0.005 - 0.03
carbon	0.0 - 0.18
chromium	13.7 - 15.3
cobalt	14.2 - 19.0
iron	0.0 - 4.0
molybdenum	3.8 - 4.8
titanium	3.0 - 3.7

The remainder of the alloys comprises nickel and incidental impurities. The elements in the alloys are balanced to provide an N_V[4] value not in excess of about 2.35[5] according to the following equation:

$$N_V = 4.66\ (A\%\ Cr + A\%\ Mo) + 1.71\ (A\%\ Co) + 0.61\ (A\%\ Ni)$$

In the case of alloys within the board range set forth above, but not balanced to meet the required Nv value, room temperature ductility deteriorates, and creep[7] deformation increases, after prolonged exposure at elevated temperatures. Appellants state that these results are attributable to formation of a deleterious phase (known as "sigma phase") in the metal after such exposure, and that the tendency of an alloy to form sigma phase is (unexpectedly) eliminated by balancing the relative amounts of its constituent elements in accordance with the N_V equation. Where the composition of an alloy has been controlled to provide an N_V value of about 2.35 or less, no sigma has been found after exposure at 1500°F for time periods up to 7200 hours.

Claim 1 is illustrative:

1. A nickel base alloy having a composition consisting essentially of up to 0.18% carbon from about 14.2% to about 19.0% cobalt, from about 13.7% to about 15.3% chromium, from about 3.8% to about 4.8% molybdenum, from about 3.0% to about 3.7% titanium, from about 4.0% to about 4.7% aluminum, up to about 4.0% iron, from 0.005% to about 0.03% boron and the balance essentially nickel with incidental impurities, the aforementioned elements being balanced to provide an N_V value not in excess of about 2.35 according to the following equation:

$$N_V = 4.66\ (A\%\ C + A\%\ Mo) + 1.71\ (A\%\ Co) + 0.61\ (A\%\ Ni)$$

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* The Honorable Herbert N. Maletz of the United States Customs Court, sitting by designation.

[1] Serial No. 587,776 was filed on June 17, 1975.

[2] U.S. patent No. 3,147,155, issued September 1, 1964.

[3] U.S. patent No. 3,457,066, issued July 22, 1969.

[4] N_V refers to the average electron vacancy concentration per atom in the matrix of the alloy.

[5] Appellants state that the overall variation in N_V due to chemical uncertainty is +0.25 so that in reality the N+value of about 2.35 may actually extend from 2.32 to 2.38.

[6] Appellants' specification states that A% "refers to the atomic percent of the element so described."

[7] Creep is the permanent deformation of a metal that occurs as a result of prolonged compression or extension at or near room temperature. The Condensed Chemical Dictionary 228 (8th ed. 1971).

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the alloy being characterized by its freedom from precipitation of deleterious amounts of sigma-like phase after exposure at temperatures in excess of 1500°F for periods of time in excess of 1000 hours.

Prior Art

Lamb discloses a process for hot working age-hardenable nickel-chromium alloys. The alloys contain:

Metals	Percent by Weight
aluminum	4.0 - 5.4
boron	0.003 - 0.1
chromium	14.0 - 16.0
carbon	0.01 - 0.2
cobalt	14.0 - 25.0
molybdenum	3.0 - 5.5
titanium	3.0 - 4.6
zirconium	0.01 - 0.2

A sample alloy is heated at 1190°C for 1.5 hours and cooled to 1000°C at about 1°C per minute, after which it may be hot worked at 1120°C. When hot working is complete, the alloy will generally require a further heat treatment to develop full creep resisting properties.

Pohlman et al. disclose nickel base alloys suitable for elevated temperature operation containing:

Metals	Percent by Weight
aluminum	4.2 - 4.6
boron	0.025 - 0.035
carbon	0.04 - 0.07
chromium	14.5 - 15.5
cobalt	14.5 - 15.5
molybdenum	4.5 - 5.5
titanium	3.3 - 3.7

The remainder of the alloys essentially comprises nickel and incidental impurities; possibly, also, small amounts of silicon and manganese.

Both references are silent regarding an N_V value requirement, although Lamb requires "a total aluminum and titanium content from about 7.75% to about 9.5%," and Pohlman et al. "prefer abot 14.5-15.5 percent by weight cobalt because that range results in the best balance at elevated temperatures between such properties as tensile and rupture strengths, oxidation resistance and the ability of the sheet material to be formed or worked."

The Boesch Affidavit

Seven heats of alloys (appellants' Table I below), which were within the claimed composition ranges but whose N_V values varied from 2.40 to 2.54 (all clearly above the upper limit of 2.35 set forth in the claims), were processed and heat treated. Appellants' Table II shows that all seven heats contained sigma phase.

TABLE I

CHEMISTRY-WEIGHT PERCENT

Heat No.	C	Cr	Ni	Co	Fe	Mo	Ti	Al	B	N_V
D1-379-1	0.01	15.3	Bal.	17.9	--	4.5	3.6	4.7	0.023	2.53
D1-379-2	0.04	15.3	Bal.	17.9	--	4.6	3.6	4.7	0.022	2.54
D1-380-1	0.06	15.3	Bal.	17.5	1.0	4.6	3.6	4.7	0.021	2.51
D1-380-2	0.06	15.1	Bal.	17.4	3.5	4.5	3.5	4.6	0.020	2.40
D1-382	0.06	15.3	Bal.	18.5	--	4.3	3.5	4.4	0.019	2.47
D1-383	0.06	15.2	Bal.	17.7	--	4.3	3.6	4.4	0.020	2.43
D1-386	0.06	15.3	Bal.	18.1	--	4.7	3.4	4.6	0.021	2.49

TABLE II

Heat No.	Approximate w/o Sigma
D1-379-1	1.4
D1-379-2	0.9
D1-380-1	0.4
D1-380-2	0.05
D1-382	0.05
D1-383	0.3
D1-386	0.3

The affidavit states that "any amount of sigma phase is deleterious and undesirable because of the susceptibility to embrittlement failure following exposure to high temperature."

The Board

The board agreed with the examiner that the claimed alloys were prima facie obvious from the prior art, noting that there was no substantial disagreement that both Pohlman et al. and Lamb disclose alloys having compositional limits overlapping those of the claimed alloys. Although disagreeing with the examiner's contention that there was no evidence to support the statement in the Boesch affidavit that "any amount of sigma phase is deleterious and undesirable," it agreed with the examiner that the Boesch affidavit was insufficient to overcome the prima facie case of obviousness because there was no evidence showing:

> (1) the precise amounts of sigma-like phase present in compositions containing Appellants' claimed components balanced to provide Nv values just inside versus just outside Appellants' claimed "about 2.35" N_V limits; and (2) direct comparisons of sufficient mechanical properties of those compositions within and without the claimed limit, to demonstrate the alleged critical correlation of Nv limit with sigma phase content.[8]

The board also said that the showing (in the specification, set forth infra) did not establish the asserted criticality in selection of the components of the alloys according to the claimed N_V forumla, because the alloys failed to meet the claimed compositional and N_V value requirements.

Opinion

The Prima Facie Case

Each of the ranges of constitutents in appellants' claimed alloys overlaps ranges disclosed by Pohlman et al. and Lamb. Appellants, citing In re Waymouth, 499 F.2d 1273, 182 USPQ 290 (CCPA 1974), argue that neither of the cited prior art references recognizes the problem solved by them and, therefore, cannot render the claims obvious. Upon examination of the prior art references, we do not agree. Appellants admitted in their specification that:

> It has been postulated according to Pauling's theory that the criterion for the formation of sigma phase is based upon the number of electron vacancies (N_V) in the bonding orbitals of the elements involved. Based thereon, other investigators have derived an empirical equation which includes the elements chromium, molybdenum, manganese, iron, cobalt and nickel. It is to be noted, however, that the nickel base alloys to which reference is made in the present invention relate to an iron-free or low-iron composition, with only incidental amounts of an element such as manganese, and are hardened by the aluminum and titanium rich intermetallic compound gamma prime.

U.S. patent No. 3,837,838 ('838), filed December 18, 1972, and issued September 24, 1974, was introduced into evidence by appellants and further illuminates what is meant by "Pauling's theory":

> As described in an article by Linus Pauling entitled "The nature of interatomic forces in metals," published in Physical Review, 54:899, 1938, in a given metallic atom, the outer most orbitals, termed the bonding orbitals, are occupied by the bonding electrons responsible for bonding the atom to its neighboring metallic atoms. At a given instant in time and on the average, the bonding orbitals

[8] The board agreed with the examiner that "there [was no evidence showing] that an alloy having an N_V number of 2.35 is free of any amount of sigma phase, or what the sigma phase content and properties are of an alloy having an N_V number of 2.36 which is close to but outside the N_V requirement."

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are only partially occupied by the bonding electrons. Such partial occupation means that the outer orbitals are partially vacant of electrons or possess an "electron hole." The total average number of vacant orbitals in a given metallic atom is called the electron hole number of the metal (N_V). The average electron hole number (N_V) is the resultant of adding all Nv for the participating elements in the alloy matrix. The higher the N_V of a given Co-Cr-Ni alloy the higher the chance for the precipitation of embrittling phases. The quantities of metals consumed in precipitation do not enter in calculating N_V of the alloy matrix and hence do not participate in the formation of embrittling phases. A low N_V may thus be obtained by either choosing elements of low N_V to form an alloy or by using elements that will react in the alloy and precipitate out from the alloy matrix.

Accordingly, in carrying out this invention, I have selected an alloy-base for the system which possesses a low N_V, and have strengthened the alloy base by adding elements which will have minor or no effect on raising the N_V through controlling their percentage as solutes or by eliminating their effect on N_V by formation of compounds which precipitate out.

It appears from appellants' specification that certain precipitate-hardened nickel base alloys, after being exposed to elevated temperatures for prolonged periods of time, suffered "from a marked and catastrophic decrease in room temperature ductility and a marked increase in the rate of creep deformation." It was observed that other nickel base alloys having the same percentage ranges of components did not suffer such deleterious changes. The cause of the problem was believed to be the formation of an embrittling phase ("sigma"). As early as 1938, however, it was known that the higher the N_V value of a Co-Cr-Ni alloy, the higher the chance for precipitation of embrittling phases; also, that the quantities of metals consumed in precipitation did not enter into calculating the N_V value of an alloy matrix. We are persuaded that one of ordinary skill in the art would have been guided by these principles.

[1] In the above-quoted passage from '838, we note that lowering the N_V value of a Co-Cr-Ni alloy and deletion of the metals not consumed in precipitation from the N_V calculation are expressly suggested. Considering, also, that the composition requirements of the claims and the cited references overlap, we agree with the Solicitor that the prior art would have suggested "the kind of experimentation necessary to achieve the claimed composition, including the proportional balancing described by appellants' Nv equation." This accords with the rule that discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977); In re Aller, 42 CCPA 824, 220 F.2d 454, 105 USPQ 233 (1955). Accordingly, we conclude that a prima facie case of obviousness has been established.

Unexpected Results

[2] It is well settled that a prima facie case of obviousness may be rebutted "where the results of optimizing a variable, which was known to be result effective, [are] unexpectedly good." In re Antonie, supra, 559 F.2d at 620, 195 USPQ at 8-9, and cases cited therein. It is also well settled that proof of unexpected properties may be in the form of direct or indirect comparative testing of the claimed compounds (here, alloys) and the closest prior art. In re Payne, 606 F.2d 303, 316, 203 USPQ 245, 256, (CCPA 1979), and cases cited therein.

A. Creep Tests

Table V, set forth in appellants' specification and shown below, compares four examples of the claimed alloys with one example (6-3211) of a prior art alloy and is intended to show that the measured creep of the claimed alloys is unexpectedly less than that of the prior art.

TABLE V

Creep Tests at 1500°F and 37,000 psi

Alloy No.	Sample Removed After (Hours)	Measured Creep (inches per inch)
2-1422	1567.8	0.008
2-1423	1500.4	0.004
2-1425	1504.5	0.010
2-1426	1500.4	0.004
6-3211	1505.1	0.034

The measured creep of 6-3211 — an alloy, appellants note, having "chemistries" within those of the references — is in excess of three to eight times greater than the creep of the claimed alloys.

The composition and N_V values of the alloy heats in Table V are as follows:

Alloy No.	Element, Weight % C	Al	Ti	Mo	Cr	Co	B	Ni	Nv Value
2-1422	0.07	4.20	3.23	4.70	14.7	18.0	0.030	bal.	2.32
2-1423	0.06	4.37	3.45	4.45	14.6	17.6	0.028	bal.	2.36
2-1425	0.06	3.91	2.98	4.40	14.8	17.5	0.028	bal.	2.21
2-1426	0.05	4.20	3.19	4.50	14.5	17.5	0.030	bal.	2.27
6-3211	0.06	4.43	3.54	4.95	15.2	18.8	0.030	bal.	2.51

Although it is apparent that the molybdenum content of 6-3211 exceeds the maximum content of the claimed alloys by 0.15%, it is clearly within the ranges of the Pohlman et al. and Lamb alloys.

[3] However, we are not persuaded that the Table V data are commensurate in scope with appellants' claims. In re Greenfield, 571 F.2d 1185, 1189, 197 USPQ 227, 230, (CCPA 1978).[9] Appellants claim broad ranges of elements, but the weight percent of elements in the four examples of the claimed alloys vary by relatively minor amounts. For example, the entire *claimed* range of carbon is .18 percent, but the *tested* range is only .02 (.07 minus .05); the claimed cobalt range is 4.8, but the test range is only 1.3. There is no evidence showing whether other alloys encompassed by appellants' broad claims and having elements varying by relatively major amounts also exhibit a low creep rate.

B. Ductility Test

Appellants' Table VI, set forth in their specification, compares the room temperature ductility of one heat of the claimed alloy (2-1426) and one heat of an alloy (6-3266) which appellants state has "chemistries" within those of the references.

TABLE VI

Room Temperature Tensile Tests

Alloy No.	Condition	U.T.S. psi	0.2% Offset Y.S. (psi)	Elong. (%)	R.A. (%)	Nv Value
2-1426	As-heat-treated	204,000	140,000	16.9	15.0	2.27
2-1426	As-heat-treated + exposed 5000 hrs. at 1500°F	157,000	100,000	16.1	14.1	2.27
6-3266	As-heat-treated	194,500	136,800	14.0	13.7	2.52
6-3266	As-heat-treated + exposed 5000 hrs. at 1500°F	150,500	117,500	5.0	5.5	2.52

The marked decrease in room temperature ductility (Elong.) after prolonged elevated temperature exposure of the prior art alloy (6-3266), compared to the claimed alloy's (2-1426) essentially unchanged ductility, is contended to show an unexpected result, as was the improvement in measured creep discussed earlier. However, for the same reason that the measured creep test data of Table V are not persuasive of unexpected results, we do not regard the tensile test data of Table VI, comparing only one heat of a claimed alloy, sufficient to rebut the prima facie case of obviousness of the claimed invention.

C. Absence of Sigma Phase

Throughout prosecution appellants have maintained that the claims define "a nickel base alloy which can be manufactured in a consistent way to remain free from a tendency to form plate-like sigma phase." The "essential concept of the present invention [is] to maintain the average number of electron vacancies at a value not exceeding about 2.35." Whereas the Pauling theory teaches that a low N_V value means *reduced chances* for sigma phase, appellants allege that alloys meeting their composition and N_V value requirements are *free* from sigma phase.

[4] As related earlier, the Boesch affidavit shows that sigma phase is present in

[9] It is unnecessary to decide whether 6-3211 is the "best prior art." See In re Malagari, 499 F.2d 1297, 1302-03, 182 USPQ 549, 552-53 (CCPA 1974).

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1	14.1	2.27
0	13.7	2.52
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seven alloy examples, all of which meet the composition requirements but exceed the N_V value requirement of the claimed alloys. However, this affidavit contains no examples of claimed alloys showing the absence, or presence, of sigma. The remainder of the record reveals only a single example of the claimed alloy, which shows the absence of sigma.[10] Appellants' specification includes a photomicrograph of Table V alloy heat 2-1422, which clearly shows the absence of sigma; also, a photomicrograph of Table V alloy heat 6-3211, which shows the presence of sigma. We note again that the prior art teaches that reduction of the N_V value *reduces the chances* of sigma phase in the alloy. Here appellants tested only one example of a low N_V value alloy and found no sigma — a result consistent with both the prior art teaching and appellants' allegation that their claimed alloys are "totally *free* from sigma phase."[11] Under such circumstances, test results involving a single alloy within the broad range claimed are not sufficient to support appellants' allegation of what would, from the prior art, be unexpected.[12]

In view of the foregoing we hold that appellants have failed to rebut the prima facie case of obviousness.

The decision of the board is *affirmed.*

Affirmed.

[10] Thus, appellants have again failed to show test data commensurate in scope with the broad claims.

[11] We agree with the board that the six United States patents ((1) No. 4,093,474, issued June 6, 1978; (2) No. 4,083,734, issued April 11, 1978; (3) No. 3,930,904, issued January 6, 1976; (4) No. 3,837,838, issued September 24, 1974; (5) No. 3,816,110, issued June 11, 1974; and (6) No. 3,767,385, issued October 23, 1973) introduced into the record by appellants "do support the assertion in the Boesch affidavit that 'any amount of sigma phase' is undesirable." Therefore, we have limited our analysis to the issue of the existence of sigma phase and have not extended it to include the effect of varying amounts of sigma phase.

[12] Where it is alleged that a certain technique for flipping coins would always produce "heads," one would hardly be persuaded by a single toss of a coin which resulted in a showing of "heads."

Court of Customs and Patent Appeals

In re Breslow

No. 79-602

Decided Feb. 28, 1980

PATENTS

1. Patent grant — In general (§50.01)

Patent grant — Nature of patent rights — In general (§50.201)

Government grants only right to exclude; there is no other agreement; analogy of a patent to a contract on theory that it is issued in exchange for invention's disclosure, "consideration," is inexact; patent is statutory right; it is granted to "Whoever" fulfills conditions, Section 101, unless fraud has been committed.

2. Court of Customs and Patent Appeals — Issues determined — Ex parte patent cases (§28.203)

Question of whether claimed compounds "are even formed" on which point Board of Appeals disagreed with examiner who argued that there was no indication nor proof on this point and board expressly held to contrary is not before Court of Customs and Patent Appeals.

3. Patentability — Subject matter for patent monopoly — In general (§51.601)

Ex parte Howard, 328 O.G. 251, 1924 C.D. 75, dealt with construction of "manufacture" rather than "composition of matter," with gob, of at least obvious, molten glass in transitory state rather than with novel chemical compounds, and with mechanical molding process in which it was well known to use molten gob of glass as distinguished from novel chemical process using entirely new and unobvious group of chemical compounds.

4. Patentability — New use or function — Composition of matter (§51.555)

Patentability — Subject matter for patent monopoly — In general (§51.601)

In re Stubbs, 13 USPQ 358, did not deal with issue of whether claimed compounds are excluded from category of "composition of matter" in Section 101 merely because they are transitory, unstable, and non-isolatable.

5. Patentability — New use or function — Composition of matter (§51.555)

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award of fees and costs was not proper unless Atrana was a prevailing party. 35 U.S.C. § 285 (2000). Atrana cannot be a prevailing party if the case was resolved by settlement (not incorporated by judicial decree) prior to any relief on the merits. *See Akers v. Nicholson*, 409 F.3d 1356, 1359 (Fed. Cir. 2005); *Inland Steele Co. v. LTV Steel Co.*, 364 F.3d 1318, 1320-21 [70 USPQ2d 1472] (Fed. Cir. 2004). For this reason, we vacate this award so that the district court can reconsider its attorney fees and costs determination after it has determined the enforceability of the settlement agreement. If it were to reaffirm its award of costs and fees, an appeal would, of course, be available to this court.

CONCLUSION

For the foregoing reasons, the decision below is affirmed in part, reversed in part, vacated in part, and remanded for further proceedings.

AFFIRMED-IN-PART, REVERSED-IN-PART, VACATED-IN-PART, and REMANDED-IN-PART

COSTS

No costs.

In re Kahn

U.S. Court of Appeals
Federal Circuit

No. 04-1616

Decided March 22, 2006

PATENTS

[1] Practice and procedure in Patent and Trademark Office — Board of Patent Appeals and Interferences — In general (§ 110.1101)

Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Patentability/Validity — Obviousness — Evidence of (§ 115.0906)

Problem to be examined in considering motivation to combine prior art references is not specific problem solved by invention at issue, but general problem that confronted inventor before invention was made; thus, "motivation-suggestion-teaching" test asks not merely what references disclose, but whether person of ordinary skill in art, possessed with understandings and knowledge reflected in prior art and motivated by general problem facing inventor, would have been led to make claimed combination, and from this it may be determined whether overall disclosures, teachings, and suggestions of prior art, and level of skill in art, support legal conclusion of obviousness.

[2] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Substantial evidence supports conclusion that person of ordinary skill in art would have been motivated to combine teachings of prior art patent, which claims acoustical imaging system for use by visually impaired individuals, with teachings of two primary references to achieve invention of application claiming "reading machine" for use by blind persons, since prior patent teaches that its invention relates to augmentation of vision of those who have lost vision or have had their visual faculties diminished, that it is useful in teaching such persons "to apprehend the position of a virtual sound source as representing a point in space," and that it may be used as "rudimentary reading device," and since skilled artisan, who knows of "learning machine" that is capable of reading word aloud by selecting word on screen at which user is looking and seeks to provide visually-impaired user better control over word localization, would have reason to solve that problem by adding two-dimensional sound, in view of prior patent's express teaching that two-dimensional sound can be used to "substitute" for lost sense of sight, to locate point in space, and to create "rudimentary reading device" for visually impaired persons.

[3] Patentability/Validity — Obviousness — Person of ordinary skill in art (§ 115.0902)

Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Board of Patent Appeals and Interferences did not overstate knowledge of person of ordinary skill in art, or employ improper hindsight, in making prima facie case of obviousness, since motivation to combine prior art

references to achieve invention claimed in application was articulated and placed on record.

[4] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Applicant's contention that person of ordinary skill in art would not have been motivated to combine prior art references to achieve invention claimed in application is without merit, since, even if applying secondary reference to primary reference resulted in device that would be less effective for primary reference's intended purpose, teaching of that reference is not limited to specific invention disclosed therein, since applicant may have envisioned something different from skilled artisan in considering secondary reference, but artisan need not be motivated to combine secondary reference for same reason contemplated by applicant, and since secondary reference does not teach away from combination with primary reference, as there is nothing in secondary reference that would discourage person of skill in art from using device taught in primary reference in claimed combination, or that would lead skilled artisan in direction divergent from path taken by applicant.

[5] Patentability/Validity — Obviousness — Long felt need (§ 115.0909)

Appellate court will not take judicial notice of long-felt need for device claimed in patent application, which is intended to help blind persons read, since finding either way on question of long-felt but unresolved need can reasonably be questioned, and long-felt need thus is not type of undisputed fact susceptible of judicial notice, and since precedent requires that applicant submit actual evidence of long-felt need, as opposed to argument, in that mere passage of time without claimed invention is not evidence of nonobviousness.

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Application of Leonard R. Kahn for patent on "reading machine" for use by blind persons. Applicant appeals from decision upholding rejection of claims in application for obviousness under 35 U.S.C. § 103. Affirmed.

Leonard R. Kahn, New York, N.Y., pro se.

John M. Whealan, solicitor; Linda Moncys Isacson and Raymond T. Chen, associate solicitors, and Mary L. Kelly, U.S. Patent and Trademark Office, Arlington, Va., for Director, U.S. Patent and Trademark Office.

Before Michel, chief judge, and Linn and Prost, circuit judges.

Linn, J.

Leonard R. Kahn ("Kahn") appeals from the final decision of the Board of Patent Appeals and Interferences ("Board") concluding that claims 1–20 in patent application number 08/773,282 ("the '282 application") are unpatentable as obvious under 35 U.S.C. § 103.[1] Because the factual findings underlying the Board's conclusion are supported by substantial evidence, and because the Board did not commit legal error in concluding that the claims would have been obvious, we affirm.

BACKGROUND

I. A. The Invention

The '282 application, filed on December 24, 1996 as a continuation-in-part of a series of continuing applications dating back to 1989, involves a "reading machine" that may be used by the blind. Prior to the application, machines that employed memory and display components by which material could be "read" using hand-held optical pens and speech synthesizers were known in the art. While a user can control these devices by hand to repeat words and to read at various speeds, such control is cumbersome, which makes it difficult for a blind user to study complex publications. Kahn addressed this problem and claims invention in a device that is operated by eye control and sound localization such that it can read out loud the word "looked at" by the user.

Kahn treats claims 1–20 as a group with claim 1 being representative:

> 1. A reading machine suitable for use by totally blind individuals for reading the complete text, or a selected portion thereof, of a document stored in storage means, at the option of the user, comprising:

[1] The Board also affirmed its own rejection of claims 21 and 22 as being non-enabled under 35 U.S.C. § 112, ¶ 1; however, in his opening brief on appeal Kahn withdrew those claims, leaving only claims 1–20 before us.

(a) means of storing at least a portion of the text of the document to be read,

(b) means for retrieving a selected portion of said stored text made available for immediate "reading,"

(c) means for producing an acoustical display of the selected portion of said stored text, in a page-like format,

(d) means for determining the location on the acoustical display towards which the user is "looking," and

(e) means for generating speech sounds verbalizing the word that is formatted to appear on the acoustical display at the location the user is "looking" towards.

A preferred embodiment of the '282 patent is illustrated below in Figure 1.

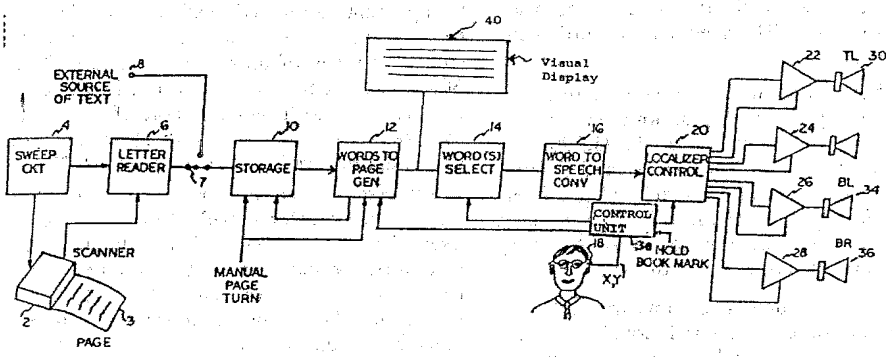

FIG.1

In operation,

[t]he information being "read" . . . is fed through intermediate storage means to speech synthesizer means for converting the written information to electrical waves representing speech sounds. These electric waves are fed to . . . a four speaker array wherein the speakers are located in a fashion so that the artificial sound image can be placed at various points on the artificial screen or page allowing the user to hear the words at the desired locations. These locations would be selected by the user looking at a specific location on the artificial screen or page.

The user would then move his or her eyes to "look" where the next word would be expected to appear, i.e., directly to the right of the spoken word. This would then cause the next word to be "spoken" and the sound image would appear slightly to the right. This motion is achieved by energizing the four speaker array with different levels of audio power. . . .

When the user completes the "reading" of the last word on the page, . . . the reader would have the option of rereading a section on the page or causing the page to be "turned." If the user wishes to reread . . ., he can direct his attention to the material to be reread by "looking" at the portion of the page where he remembers hearing the material.

On the other hand, if he wishes to continue reading the material he can turn the page by looking along the bottom line past the right hand edge of the "page". The first word on the new page would be heard when the reader directed his or her attention to the upper left hand corner of the page where the first word on the new page would be expected.

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'282 application at 11-13.

According to the specification, the device can employ a conventional scanner to input data; a conventional character recognition device to translate and send data to a storage device; and a page generator to take data from the storage device and format it for a visual display and for a word selector, the latter of which can send the data to a conventional speech synthesizer. After an optical sensor detects where a user is "looking" and a word is "selected" for vocalization, the synthesizer feeds an audio signal to a localizer control. Loud speakers are arranged at the corners of the "page" to allow the user to confirm localization of sound. The specification further indicates that

> [t]here are a number of devices available for sensing where an individual is looking. For example, Garwin et. al. 4,595,990 . . . , Anderson et. al. 4,579,533 . . . and Stanton 4,322,744 . . . . More specifically, Anderson's [sic] patent discusses feed-back which may be visual, auditory or tactile to verify decisions by eye control equipment.
>
> However, such inventions are not suitable for totally blind individuals who are not verifying where they are looking but are using their eyes to direct which part of the artificial page should be read to produce a sound image. This makes essential a two dimensional stereo sound stage which the blind person solely depends upon.

'282 application at 16.

B. The Prior Art

The Board's rejection was based on Garwin et al., U.S. Patent No. 4,595,990 (issued June 17, 1986) ("Garwin"), in view of Anderson et al., U.S. Patent No. 4,406,626 (issued Sept. 27, 1983) ("Anderson '626"), Anderson et al., U.S. Patent No. 4,579,533 (issued April 1, 1986) ("Anderson '533"), and Stanton, U.S. Patent No. 4,322,744 (issued March 30, 1982) ("Stanton"). The Board alternatively used Anderson '626 or '533 as primary references.

Garwin discloses an eye-controlled interactive information processor that senses the portion of a visual display at which the user is looking. The processor is connected to the display, which, in turn, can be partitioned so that different information is displayed in discrete areas. By gazing in different directions, the user informs the processor of the displayed item that is selected. Garwin, col. 2, ll. 60-68. The preferred embodiment employs a reflected light eye-tracking device to determine where the user is looking. *Id.*, col. 3, l. 66–col. 4, l. 62. The eye-interactive control generally uses a technique where the user is presented with a number of targets having some meaning, such as "words or phrases" displayed on screen. *Id.*, col. 9, ll. 62-67. "Visual, auditory or tactile" feedback is then given to the user to indicate that a selection has been received. *Id.*, col. 2, ll. 10-11; col. 11, ll. 59-64. The user then can verify or cancel the selection. *Id.*, col. 10, ll. 1-6. Garwin states that "it will be apparent to one skilled in the art that . . . the benefits of the invention will be achieved by many types of apparatus." *Id.*, col. 2, ll. 50-53. It can be used for "request[ing] display of a page of text from a . . . table of contents," *id.*, col. 3, ll. 42-44, or "[other] presentation of textual material," *id.*, col. 10, ll. 31-33.

Anderson '626 discloses an interactive "electronic teaching aid" which enables a user viewing text on a display to designate any words or portion of text for immediate audible vocalization. Anderson '626, col. 1, l. 8; col. 2, ll. 11-17. The components include: a selector switch, which when in the "text" position, causes data to be transmitted to a monitor and displayed in legible form, *id.*, col. 3, ll. 27-31; an advance button, which when depressed allows the user to select and retrieve the next page of text from memory, *id.*, col. 3, ll. 31-41; a memory, which can store each word of the text coded for speech, *id.*, col. 3, l. 66–col. 4, l. 6; and a word designator light pen, which the user can place on a word to hear the word vocalized through the speaker, *id.*, col. 3, ll. 54-68; col. 10, ll. 51-58. Anderson '533 discloses an improved microprocessor-based version of Anderson '626. Anderson '533, col. 1, ll. 19-24, 41-56.

Stanton discloses an acoustical imaging system for use by visually impaired individuals that uses horizontal and vertical directional sound to represent visual aspects of an environment. Stanton states that a user can locate "the position of a virtual sound source as representing a point in space" such that different signals may represent different directions. Stanton, col. 1, ll. 58-61. The preferred embodiment features four loud speakers or transducers mounted at the corners of a vertical display panel. *Id.*, col. 2, ll. 54-55. When the user moves the cursor, the sound emanating

from the speakers is phase shifted to produce a virtual sound seeming to come from a particular location related to the position of the cursor. *Id.*, col. 1, l. 66–col. 2, l. 2; col. 2, ll. 55-63. In another embodiment, a quadraphonic headset is used in place of the transducers to achieve the effect of producing a virtual sound identifying a position. *Id.*, col. 4, ll. 26-35. Stanton states that the device may be used as a "rudimentary reading device." *Id.*, col. 1, ll. 62.

C. The Board Decisions

Kahn filed the '282 application with 22 claims as a continuation-in-part of application number 07/645,102 ("the '102 application"), which was filed in 1991. The '102 application was a continuation-in-part of a series of abandoned continuing applications dating back to application number 07/338,597, which was filed in 1989. While claims 21 and 22 of the '282 application are not at issue in this appeal, the Board addressed those claims on several occasions, which led to the creation of a substantial Board history. As a result, the final decision with respect to the obviousness rejection of claims 1–20 spans three decisions, which include *Ex Parte Kahn*, No. 2004-1091 (B.P.A.I. June 30, 2004) ("*2004 decision*"); *Ex Parte Kahn*, No. 2000-1130 (B.P.A.I. Feb. 24, 2003) ("*2003 decision*"); and *Ex Parte Kahn*, No. 94-2233 (B.P.A.I. Sept. 21, 1995) ("*1995 decision*").

In its 1995 decision, after reversing the examiner's anticipation rejection, the Board *sua sponte* rejected the relevant claims under § 103. The Board found that Garwin taught "the concepts of determining where on a display screen a user is 'looking' . . . and giving either visual or *auditory* feedback to the user" and that "[w]hile nothing specific is said as to acoustically reproducing a word displayed at that location, common sense . . . indicate[s] that such an auditory feedback response is appropriate in view of such *auditory* feedback confirmation clearly suggested by Anderson '533 or '626." *1995 decision*, slip op. at 5 (emphasis in original). The Board found that "to whatever extent Garwin is not concerned with text *per se*, [the Anderson] references are" and "teach the advantages of text display with audio reproduction," concluding that

> the artisan would have found it to have been obvious to have modified Garwin for display of text passages and selection of works therefrom with vocalization thereof as feedback confirmation, all as taught by Anderson '626 or '533 . . . [or] to have modified either of these Anderson references to use the eye control of Garwin so that the user's hands would have been free for other tasks.

Id., slip op. at 5-6. The Board found that Stanton "teaches the benefit of acoustic imaging in reading systems" and that "[i]t would have, thus, been further obvious to the artisan to add advantageous acoustic imaging to either of the above-noted modified devices of Garwin or the Anderson patents which would have word positions acoustically and visually indicated." *Id.*, slip op. at 6.

In its *2003 decision*, the Board expressly incorporated the findings and rationale from both its *1995 decision* and the Examiner's Answer filed on April 24, 2000. *2003 decision*, slip op. at 3-4. In the Answer, the Examiner had explained that Garwin teaches "a buffer memory which stores at least a portion of the information derived from sensing means and means for subsequently retrieving the sensed information," "means for displaying stored written text," and "means for determining which word of the displayed text the user is looking towards"; that Anderson '626 teaches "means for generating speech sounds verbalizing the looked at word"; and that Stanton teaches "means for verbalizing each word the user's eyes are directed towards in two dimensional stereo." Examiner's Answer at 5-6. Rejecting Kahn's argument that hindsight drove the combination of references, the Board reiterated that the rationale of the 1995 decision was correct and explained that motivation "clearly is based upon a prospective look at the state of the art." *2003 decision*, slip op. at 8-11.

The Board addressed several other arguments. First, the Board rejected the argument that the invention's intended use supports patentability, noting that "the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus [from] a prior art apparatus satisfying the claimed structural limitations." *Id.* at 5-6. Second, the Board rejected the argument that because "the purposes of the [prior art] references . . . are different from the [invention's] purpose," the invention is non-obvious, explaining that "[t]he law . . . does not require that references be combined for reasons con-

templated by an inventor" and that "prior art need not suggest the same problem set forth by appellant." *Id.* at 6-7. Third, the Board rejected the arguments that features of a secondary reference be capable of incorporation into the structure of a primary reference and that the invention be suggested completely by one reference. *Id.* at 7. Finally, the Board rejected a "long-felt need" argument, explaining that Khan had not presented any objective evidence of a long-standing problem or long-standing need in the art. *Id.* at 11-12.

In its *2004 decision*, the Board entered a final rejection of claims 1–20 based on its *2003 decision*. Kahn timely appealed to this court. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(4)(A).

II. DISCUSSION

A. The Parties' Arguments

Khan advances two main arguments. First, Khan asserts that the Board's finding of motivation to combine was unsupported by substantial evidence. Citing *In re Lee*, 277 F.3d 1338 [61 USPQ2d 1430] (Fed. Cir. 2002), and *In re Rouffet*, 149 F.3d 1350 [47 USPQ2d 1453] (Fed. Cir. 1998), Khan argues that the Board overstated the knowledge of the skilled artisan and employed improper hindsight. Specifically, Khan asserts that a skilled artisan would not have sought to augment Garwin with sound because the resulting device would be more expensive and less reliable for the purpose intended by Garwin. He contends that just because Stanton teaches use of sound to confirm a visual perception of a shape like a letter—which provides a "rudimentary" reading capability—does not mean that the reference teaches how to enable a blind user to "read" and "reread" entire words and phrases quickly. Khan further contends that Stanton teaches away from a system that employs iris eye direction sensing because Stanton requires the user to hold his head steady, because eyes are not involved in its localization procedure, and because the combined device would be expensive and inoperable. Second, Khan argues that the court should take "judicial notice" that his reading machine addresses a "long-felt, but unresolved need," and that this consideration is sufficient to rebut a *prima facie* case of obviousness.

The Patent and Trademark Office ("PTO") counters that *Lee* and *Rouffet* are distinguishable because here the Board identified motivations to combine the references based on specific statements in the references and on the nature of the problem to be solved. As to long-felt need, the PTO argues that Kahn proffered no actual evidence, and that Kahn's argument alone is insufficient to rebut a *prima facie* case.

B. Standard of Review

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. 35 U.S.C. § 103(a) (2000); *Graham v. John Deere Co.*, 383 U.S. 1, 13-14 [148 USPQ 459] (1966). The ultimate determination of whether an invention would have been obvious is a legal conclusion based on underlying findings of fact. In re *Dembiczak*, 175 F.3d 994, 998 [50 USPQ2d 1614] (Fed. Cir. 1999). We review the Board's ultimate determination of obviousness *de novo*. *Id.* However, we review the Board's underlying factual findings, including a finding of a motivation to combine, for substantial evidence. *In re Gartside*, 203 F.3d 1305, 1316 [53 USPQ2d 1769] (Fed. Cir. 2000).

Substantial evidence is something less than the weight of the evidence but more than a mere scintilla of evidence. *Id.* at 1312 (citing Consol. *Edison Co. v. NLRB*, 305 U.S. 197, 229-30 (1938)). It means such relevant evidence as a reasonable mind might accept as adequate to support a conclusion. *Consol. Edison*, 305 U.S. at 229-30. In reviewing the record, we must take into account evidence that both justifies and detracts from the factual determinations. *Gartside*, 203 F.3d at 1312 (citing *Universal Camera Corp. v. NLRB*, 340 U.S. 474, 487-88 (1951)). We note that the possibility of drawing two inconsistent conclusions from the evidence does not prevent the Board's findings from being supported by substantial evidence. *Id.* Indeed, if a reasonable mind might accept the evidence as adequate to support the factual conclusions drawn by the Board, then we must uphold the Board's determination. *Id.*

C. Analysis

In assessing whether subject matter would have been non-obvious under § 103, the Board follows the guidance of the Supreme

Court in *Graham v. John Deere Co.* The Board determines " 'the scope and content of the prior art,' " ascertains " 'the differences between the prior art and the claims at issue,' " and resolves " 'the level of ordinary skill in the pertinent art.' " *Dann v. Johnston*, 425 U.S. 219, 226 [189 USPQ 257] (1976) (quoting *Graham*, 383 U.S. at 17). Against this background, the Board determines whether the subject matter would have been obvious to a person of ordinary skill in the art at the time of the asserted invention. *Graham*, 383 U.S. at 17. In making this determination, the Board can assess evidence related to secondary indicia of non-obviousness like "commercial success, long felt but unresolved needs, failure of others, etc." *Id.*, 383 at 17-18; *accord Rouffett*, 149 F.3d at 1355. We have explained that

> [t]o reject claims in an application under section 103, an examiner must show an unrebutted *prima facie* case of obviousness . . . . On appeal to the Board, an applicant can overcome a rejection by showing insufficient evidence of *prima facie* obviousness or by rebutting the *prima facie* case with evidence of secondary indicia of nonobviousness.

Rouffett, 149 F.3d at 1355.

Most inventions arise from a combination of old elements and each element may often be found in the prior art. *Id.* at 1357. However, mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. *Id.* at 1355, 1357. Rather, to establish a *prima facie* case of obviousness based on a combination of elements disclosed in the prior art, the Board must articulate the basis on which it concludes that it would have been obvious to make the claimed invention. *Id.* In practice, this requires that the Board "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious." *Id.* at 1357-59. This entails consideration of both the "scope and content of the prior art" and "level of ordinary skill in the pertinent art" aspects of the *Graham* test.

When the Board does not explain the motivation, or the suggestion or teaching, that would have led the skilled artisan at the time of the invention to the claimed combination as a whole, we infer that the Board used hindsight to conclude that the invention was obvious. *Id.* at 1358. The "motivation-suggestion-teaching" requirement protects against the entry of hindsight into the obviousness analysis, a problem which § 103 was meant to confront. *See* 35 U.S.C. § 103 (stating that obviousness must be assessed "at the time the invention was made"); *Dembiczak*, 175 F.3d at 998 ("[I]t is this phrase that guards against entry into the tempting but forbidden zone of hindsight." (internal quotations omitted)); Giles S. Rich, *Laying the Ghost of the Invention Requirement*, 1 APLA Q.J. 26-45 (1972), *reprinted in* 14 Fed. Cir. B.J. 163, 170 (2004) ("To protect the inventor from hindsight reasoning, *the time is specified to be the time when the invention was made.*") (emphasis in original). The Supreme Court recognized the hindsight problem in *Graham* and proposed that "legal inferences" resulting from "secondary considerations" might help to overcome it. 383 U.S. at 36 ("[Secondary considerations] may also serve to guard against slipping into use of hindsight, and to resist the temptation to read into the prior art the teachings of the invention in issue." (internal quotations omitted)). By requiring the Board to explain the motivation, suggestion, or teaching as part of its *prima facie* case, the law guards against hindsight in all cases—whether or not the applicant offers evidence on secondary considerations—which advances Congress's goal of creating a more practical, uniform, and definite test for patentability. *See Dann*, 424 U.S. at 225-26 ("[I]t was only in 1952 that Congress, in the interest of 'uniformity and definiteness,' articulated the requirement in a statute." (quoting S. Rep. No. 1979, at 6 (1952); H.R. Rep. No. 1923, at 7 (1952))); *Graham*, 383 U.S. at 17 ("The § 103 [test], when followed realistically, will permit a more practical test of patentability.").

Although our predecessor court was the first to articulate the motivation-suggestion-teaching test, a related test—the "analogous art" test—has long been part of the primary *Graham* analysis articulated by the Supreme Court. *See Dann*, 425 U.S. at 227-29; *Graham*, 383 U.S. at 35.[2] The analogous-art test

[2] In *Graham*, Cook Chemical challenged the court's reliance on a reference that it believed was not in a "pertinent prior art," arguing that while the invention involved a container having a "pump sprayer," the reference related to containers having "pouring spouts." 383 U.S. at 35. In reaching the conclusion that the

requires that the Board show that a reference is either in the field of the applicant's endeavor or is reasonably pertinent to the problem with which the inventor was concerned in order to rely on that reference as a basis for rejection. *In re Oetiker*, 977 F.2d 1443, 1447 [24 USPQ2d 1443] (Fed. Cir. 1992). References are selected as being reasonably pertinent to the problem based on the judgment of a person having ordinary skill in the art. *Id.* ("[I]t is necessary to consider 'the reality of the circumstances,'—in other words, common sense—in deciding in which fields a person of ordinary skill would reasonably be expected to look for a solution to the problem facing the inventor." (quoting *In re Wood*, 599 F.2d 1032, 1036 [202 USPQ 171] (C.C.P.A. 1979))). We have explained that this test begins the inquiry into whether a skilled artisan would have been motivated to combine references by defining the prior art relevant for the obviousness determination, and that it is meant to defend against hindsight. *See id.*; *In re Clay*, 966 F.2d 656, 659-60 [23 USPQ2d 1058] (Fed. Cir. 1992).[3]

The motivation-suggestion-teaching test picks up where the analogous art test leaves off and informs the *Graham* analysis. To reach a non-hindsight driven conclusion as to whether a person having ordinary skill in the art at the time of the invention would have viewed the subject matter as a whole to have been obvious in view of multiple references, the Board must provide some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct. The requirement of such an explanation is consistent with governing obviousness law, *see* § 103(a); *Graham*, 383 U.S. at 35; *Dann*, 425 U.S. at 227-29, and helps ensure predictable patentability determinations.

A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art, as

> the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.

In re Kotzab, 217 F.3d 1365, 1370 [55 USPQ2d 1313] (Fed. Cir. 2000) (internal citations omitted). However, rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. See *Lee*, 277 F.3d at 1343-46; *Rouffett*, 149 F.3d at 1355-59. This requirement is as much rooted in the Administrative Procedure Act, which ensures due process and non-arbitrary decisionmaking, as it is in § 103. *See id.* at 1344-45.

[1] In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention but the general problem that confronted the inventor before the invention was made. *See, e.g., Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323 [76 USPQ2d 1662] (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."); *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1372 [56 USPQ2d 1065] (Fed. Cir.

claimed subject matter was obvious, the Court rejected Cook's argument, explaining that the problem to be solved was a mechanical closure problem and that a closure device in such a closely related art was a pertinent reference. *Id.* Similarly, in *Dann*, the invention involved the use of automatic data processing equipment to analyze transactions within a single bank account. 425 U.S. at 227-28. The Dirk reference that the Court relied upon in making its obviousness case involved a similar system used in a non-banking context. *Id.* at 228. Citing *Graham*, the Court explained that a person of ordinary skill in the art would be aware of this reference and the Court could rely upon it in making its obviousness case because "[w]hile the Dirk's invention is not designed specifically for application to the banking industry many of its characteristics and capabilities are similar to those of respondent's system." *Id.* at 229.

[3] In *In re Clay*, we reasoned that

> [i]f a reference disclosure has the same purpose as the claimed invention, the reference relates to the same problem, and that fact supports use of that reference in an obviousness rejection. An inventor may well have been motivated to consider the reference when making his invention. If it is directed to a different purpose, the inventor would accordingly have had less motivation or occasion to consider it.

966 F.2d at 659-60. In *In re Oetiker*, we held that "the combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a *prima facie* case of obviousness." 977 F.2d at 1447.

2000) ("Although the suggestion to combine references may flow from the nature of the problem, '[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.' " (internal citation omitted) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 [45 USPQ2d 1977] (Fed. Cir. 1998))); *In re Beattie*, 974 F.2d 1309, 1312 [24 USPQ2d 1040] (Fed. Cir. 1992) ("[T]he law does not require that the references be combined for the reasons contemplated by the inventor."); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 [75 USPQ2d 1051] (Fed. Cir. 2005) (characterizing the relevant inquiry as "[would] an artisan of ordinary skill in the art at the time of the invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention,[ ] have selected the various elements from the prior art and combined them in the manner claimed"); *see also Graham*, 383 U.S. at 35 (characterizing the problem as involving mechanical closures rather than in terms more specific to the patent in the context of determining the pertinent prior art). Therefore, the "motivation-suggestion-teaching" test asks not merely what the references disclose, but whether a person of ordinary skill in the art, possessed with the understandings and knowledge reflected in the prior art, and motivated by the general problem facing the inventor, would have been led to make the combination recited in the claims. *See Cross Med. Prods.*, 424 F.3d at 1321-24. From this it may be determined whether the overall disclosures, teachings, and suggestions of the prior art, and the level of skill in the art—*i.e.*, the understandings and knowledge of persons having ordinary skill in the art at the time of the invention—support the legal conclusion of obviousness. *See Princeton Biochemicals*, 411 F.3d at 1338 (pointing to evidence supplying detailed analysis of the prior art and the reasons one of ordinary skill would have possessed the knowledge and motivation to combine).

In this case, Khan does not dispute that each element of his claimed invention can be found in either Garwin, Anderson '533 and '626, or Stanton, or that each reference lies in the pertinent art. Nor does Khan take issue with the Board's finding that a person having ordinary skill in the art would have been motivated to modify Anderson '533 or '626 in view of Garwin, or vice versa. *See* Garwin, col. 2, ll. 50-53, col. 10, ll. 31-35 (stating that "it will be apparent to one skilled in the art that . . . the benefits of the invention will be achieved by many types of apparatus" which may be "virtually [any device] susceptible of control by a computer, including . . . [those geared] to presentation of textual material").

Rather, Khan's challenge to the sufficiency of the evidence supporting the Board's *prima facie* case is directed at the motivation to apply the teachings of Stanton to achieve the claimed invention. In the 1995 decision, the Board found that Stanton "teaches the benefit of acoustic imaging in reading systems." The Board carefully examined the Anderson/Garwin combination and recognized that a skilled artisan confronted with the problem faced by Kahn would have been led by the teaching of Stanton "to add advantageous acoustic imaging" to the Anderson/Garwin combination so that it would have "word positions acoustically and visually indicated."

[2] Stanton teaches that "[its] invention relates to augmentation of vision of those who have lost vision or have had their visual faculties diminished," col. 1, ll. 6-8, that it is "useful in teaching a deprivee to apprehend the position of a virtual sound source as representing a point in space," *id.*, ll. 58-59, and that it may be used as a "rudimentary reading device," *id.*, ll. 61-62. A skilled artisan, who knows of a "learning machine" that is capable of reading a word aloud by selecting the word on the screen at which the user is looking and seeks to provide a visually-impaired user better control over word localization,[4] would have reason to solve that problem by adding two-dimensional sound in view of Stanton's express teaching that two-dimensional sound can be used to "substitute" for the lost sense of sight, to locate a point in space, and to create a "rudimentary reading device" for the visually impaired. *See Cross Med. Prods.*, 424 F.3d at 1323 (holding that "[o]ne of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings"). Because

[4] Kahn does not argue that one of ordinary skill in the art at the time of the invention would be unaware of the nature of this problem, and there is nothing in the record to suggest this to be the case, unlike the facts in the decision of our predecessor court in *In re Sponnoble*, 405 F.2d 578 [160 USPQ 237] (C.C.P.A. 1969).

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the Board need only establish motivation to combine by a preponderance of the evidence to make its *prima facie* case, *see In re Glaug*, 283 F.3d 1335, 1338 [62 USPQ2d 1151] (Fed. Cir. 2002), we conclude that substantial evidence supports the finding of a motivation to combine the teachings of Stanton to the Anderson/Garwin combination. Although a reasonable person might reach the opposite conclusion, there is far more than a "mere scintilla" of evidence present from which a reasonable mind could find a motivation to combine.

[3] We reject Khan's argument that the Board overstated the knowledge of the person having ordinary skill in the art or employed improper hindsight in making its *prima facie* case. In both *Lee* and *Rouffet*, the Board recognized that the knowledge of the skilled artisan could provide the motivation to combine but concluded that no such knowledge was articulated and placed on the record. *Lee*, 277 F.3d at 1343-45; *Rouffet*, 149 F.3d at 1357-59. In this case, motivation to combine was articulated and placed on the record. As to the Anderson/Garwin combination, the Board identified the desire to free up the hands of the Anderson user as the problem confronted and found that Garwin itself evidenced the broad applicability of its optical controls to the claimed invention. As to the addition of Stanton, the Board identified express teachings in Stanton of "the benefit of acoustic imaging in reading systems" and properly related those teachings to the Anderson/Garwin combination.

[4] We find Khan's remaining arguments unpersuasive. First, even if applying Stanton to Garwin resulted in a device that would be less effective for the purpose intended by Garwin, the teaching of the Garwin reference is not limited to the specific invention disclosed. *See In re Heck*, 699 F.2d 1331, 1333 [216 USPQ 1038] (Fed. Cir. 1983) (explaining that "[t]he use of patents as references is not limited to what the patentees describe as their own inventions" (internal quotations omitted)). As noted above, Garwin states that his invention is intended to be applied to "virtually [any device] susceptible of control by a computer, including . . . [those geared] to presentation of textual material," Garwin, col. 2, ll. 50-53; col. 10, ll. 31-35. Second, although Khan may have envisioned something different than the skilled artisan when he looked at Stanton because Stanton teaches only a *rudimentary* reading device, the skilled artisan need not be motivated to combine Stanton for the same reason contemplated by Khan. *See In re Beattie*, 974 F.2d 1309, 1312 [24 USPQ2d 1040] (Fed. Cir. 1992) ("As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor." (citing *In re Kronig*, 539 F.2d 1300, 1304 [190 USPQ 425] (C.C.P.A. 1976))). Third, Khan's argument that Stanton itself teaches away from the combination with Garwin lacks support in the reference. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 [31 USPQ2d 1130] (Fed. Cir. 1994). Nothing in Stanton can be said to discourage a person having ordinary skill in the art from using the visual-input control taught in Garwin in the claimed combination or to lead the skilled artisan in a direction divergent from the path taken by Kahn.

[5] Finally, we note that Kahn had an opportunity to rebut the Board's *prima facie* case by offering evidence of objective indicia of non-obviousness. Khan put on no evidence, but invites this court to take "judicial notice" of the long-felt but unresolved need for a device that will help the blind read. We must decline Khan's invitation for the following reasons. First, "long-felt but unresolved need" is not the kind of undisputed fact to which courts are accustomed to taking "judicial notice" because a finding either way can "reasonably be questioned." *See* Fed. R. Evid. 201(b) ("A judicially noticed fact must be one not subject to reasonable dispute in that it is either (1) generally known within the territorial jurisdiction of the trial court or (2) capable of accurate and ready determination by resort to sources whose accuracy cannot reasonably be questioned."); *In re Fielder*, 471 F.2d 640, 642-43 [176 USPQ 300] (C.C.P.A. 1973) (declining to take judicial notice of prior art references that appellant submitted as objective evidence of non-obviousness because appellant did not offer references to the Board and they were not part of the record). Second, our

precedent requires that the applicant submit actual evidence of long-felt need, as opposed to argument. This is because "[a]bsent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 [73 USPQ2d 1225] (Fed. Cir. 2004); *accord In re Wright*, 569 F.2d 1124, 1127 [193 USPQ 332] (C.C.P.A. 1977).

III. CONCLUSION

Because the factual findings underlying the Board's analysis, including the findings on motivation to combine, are supported by substantial evidence, we conclude that the Board did not err in rejecting claims 1–20 as *prima facie* obvious. Because Khan did not rebut the Board's *prima facie* case, the Board's decision is

AFFIRMED.

Arista Records Inc. v. Flea World Inc.

U.S. District Court
District of New Jersey
No. 03-2670 (JBS)
Decided March 31, 2006

COPYRIGHTS

[1] Rights in copyright; infringement — Right to reproduction — Sound recordings (§ 213.0507)

Rights in copyright; infringement — Right to distribute copies — In general (§ 213.0901)

Plaintiff recording companies have established that vendors at flea market operated by defendants directly infringed plaintiffs' copyrights in sound recordings, since plaintiffs have submitted registration certificates and declarations attesting to plaintiffs' ownership of allegedly infringed works, and have presented voluminous evidence of infringement by various vendors at flea market, and since defendants have admitted that they provide space and facilities to vendors who have sold "pirate" and counterfeit CDs and cassettes.

[2] Rights in copyright; infringement — Right to reproduction — Sound recordings (§ 213.0507)

Rights in copyright; infringement — Right to distribute copies — In general (§ 213.0901)

Infringement pleading and practice — Contributory; vicarious liability (§ 217.08)

Plaintiff recording companies are entitled to summary judgment that corporate defendants are vicariously liable for infringement of copyrights in sound recordings stemming from vendors' sales of "pirate" and counterfeit recordings at flea market operated by defendants, since defendants issued rules expressly reserving their right to inspect merchandise offered for sale, and their personnel "police" market, since defendants prohibit sale of certain items, limit vendors' rights to display certain materials, and control who sells goods at market, since flea market thus is controlled environment where defendants have comprehensive rules governing what vendors can sell, how goods are displayed, and how vendors behave, since defendants received direct financial benefit from rental of booths to vendors selling counterfeit recordings, and vending of such recordings acted as "draw" that increased number of customers shopping at market, and since defendants therefore had right and ability to supervise or control infringing vendors, and derived financial benefit from those vendors.

[3] Infringement pleading and practice — Contributory; vicarious liability (§ 217.08)

Plaintiffs alleging that defendant flea market proprietors are liable for contributory infringement of copyrights in sound recordings stemming from vendors' sales of "pirate" and counterfeit recordings at flea market need only prove that defendants had constructive knowledge of direct infringement, and thus need not prove that defendants had knowledge of specific infringements at time they materially contributed to direct infringement; "inducement rule," which holds that party who distributes device with object of promoting its use to infringe copyright is liable for resulting acts of infringement by third parties, does not apply in present case, since rule was adopted

ır plan wheresoever they
claim damages because
ırner and T & T Invest-
ıilt their ten residences in
livision as plaintiffs built
e which they assert, as a
ɔer, foreclosed them from
selling further houses
ır floor plan in that sub-
ever, there was no evi-
tiating the premise essen-
aim, that there were any
he subdivision which could
ed for this purpose. Nor
y showing that plaintiffs
ıcial ability to construct
ıses or to purchase lots
ıey would be located. The
ısed on speculation. Mr.
ified that the value of the
ffs' floor plan by defend-
and T & T Investment
,000 to $75,000. The basis
n was the claim that these
uld receive this amount in
e sale of their ten houses.
e was no evidence to show
f any, profit defendants
the sale of their houses;
ɔh, if any, profit receiv-
ɔm would be attributable
plaintiffs' floor plan and
other factors ordinarily
) the profit derivable from
ın and sale of houses.

ıeral rule that an opinion
) more than the reasons
it is based." (Long Beach
ıist. v. Stewart, 30 Cal.2d

rcumstances noted Read's
not sufficient to sustain
damages. See Southern
. City of Los Angles, 5
8; People ex rel. Dept. of
v. Alexander, 212 Cal.App.
. Read also testified that
ɔm of the trade an archi-
% of the gross construc-
a fee for the use of his
vever, this testimony was
use of such drawings in
on of one house and did
'hat would be allowed for
e same drawings in the
f additional houses. Fur-
s obvious that the draw-
ɔ in the subject testimony
ıore than the drawings of
There was no showing
cost of creating plain-
lan design. Under these
the award of $5000 com-
ages is without support in

laim to punitive damages
the contention, as noted in

the joint pretrial statement, that defendants "acted willfully and maliciously or with indifference and disregard to any damage that plaintiffs might suffer" from defendants' infringement of plaintiffs' copyright. To sustain a claim to punitive damages upon these grounds it is necessary that the evidence establish "an intent to vex, annoy or injure" (Gombos v. Ashe, 158 Cal.App.2d 517, 527); there must be "ill will on the part of the defendant, or his desire to do harm for the mere satisfaction of doing it" (14 Cal. Jur. 2d 810); "'* * * it is the wrongful personal intention to injure that calls forth the penalty.'" (Wolfsen v. Hathaway, 32 Cal.2d 632, 647-648; Gruner v. Barber, 207 Cal. App.2d 54, 59.) The evidence in the instant case does not support imposition of punitive damages under this rule.

The judgment against defendants Turner and T & T Investment Corp. must be reversed because (1) the evidence does not support the award of $5000 compensatory damages; (2) any award of damages should be limited to detriment caused by the copyright infringement occuring before plaintiffs' general publication of their floor plan through the public showings of their Catalina Street house and the sale of that house without restriction as to the use of its floor plan; and (3) the edidence does not purport an award of punitive damages.

The reasons for reversing the judgment support the order of the trial court granting defendant Fullmer a new trial.

The judgment is reversed, and the order granting defendant Fullmer a new trial is affirmed. All defendants to recover costs on appeal.

Supreme Court of the United States

GRAHAM et al. v. JOHN DEERE COMPANY OF KANSAS CITY et al.; CALMAR, INC. v. COOK CHEMICAL COMPANY; COLGATE-PALMOLIVE COMPANY v. SAME

Nos. 11, 37, 43 Decided Feb. 21, 1966

PATENTS

1. Patentability—Invention—In general (§ 51.501)

1952 Patent Act was intended to codify judicial precedents embracing principle announced in Hotchkiss v. Greenwood, 11 How. 248; while clear language of section 103 places emphasis on inquiry into obviousness, general level of innovation necessary to sustain patentability remains the same.

2. Patent grant—In general (§ 50.01)

Federal patent power stems from Article I, Section 8 of Constitution, which is both a grant of power and a limitation; this qualified authority is limited to promotion of advances in useful arts; in exercise of patent power, Congress may not overreach restraints imposed by constitutional purpose, nor may it enlarge patent monopoly without regard to the innovation, advancement, or social benefit gained thereby; Congress may not authorize issuance of patents whose effects are to remove existent knowledge from public domain or to restrict free access to materials already available; innovation, advancement, and things which add to sum of useful knowledge are inherent requisites in patent system which must promote progress of useful arts; this is standard expressed in Constitution and it may not be ignored; within limits of constitutional grant, Congress may select policy which in its judgment best effectuates the constitutional aim; within scope established by Constitution, Congress may set out conditions and tests for patentability; it is duty of Commissioner of Patents and courts in administration of patent system to give effect to constitutional standard by appropriate application of statutory scheme of Congress.

3. Patent grant—In general (§ 50.01)

Underlying policy of patent system is that benefit to public from the thing patented must outweigh restrictive effect of limited patent monopoly.

4. Patentability—Anticipation—In general (§ 51.201)

Patentability—Invention—In general (§ 51.501)

Patentability—Utility (§ 51.75)

Under 1952 Patent Act, patentability is dependent upon novelty, utility, and nonobviousness.

5. Patentability—Invention—In general (§ 51.501)

Patentability — Tests of — Flash of genius (§ 51.705)

Section 103 of 1952 Patent Act is a statutory expression of an additional requirement (nonobviousness) for patentability, originally expressed in Hotchkiss v. Greenwood, 11 How. 248; by last sentence, Congress intended to

abolish test it believed Supreme Court announced in "flash of genius" phrase in Cuno v. Automatic, 314 U.S. 84, 51 USPQ 272; actually, "flash of genius" was mere rhetorical restatement that requirement that subject matter sought to be patented must be beyond skill of the calling; it was the device, not the invention, that had to reveal "flash of creative genius."

6. Patentability—Invention—In general (§ 51.501)

35 U.S.C. 103 was not intended by Congress to change general level of patentable invention, but was intended merely as a codification of judicial precedents embracing the Hotchkiss (11 How. 248) condition, with congressional directions that inquiries into obviousness of subject matter sought to be patented are a prerequisite to patentability.

7. Patentability—Invention—In general (§ 51.501)

Additional condition (nonobviousness) in 35 U.S.C. 103, when followed realistically, permits a more practical test of patentability; emphasis on nonobviousness is one of inquiry, not quality, and, as such, comports with constitutional strictures.

8. Patentability—Evidence of—Commercial success—In general (§ 51.4551)

Patentability — Evidence of — Delay and failure of others to produce invention (§ 51.459)

Patentability—Invention—In general (§ 51.501)

Patentability — Invention — Law or fact question (§ 51.507)

While ultimate question of patent validity is one of law, condition in 35 U.S.C. 103, which is but one of three conditions, each of which must be satisfied, lends itself to several basic factual inquiries; under section 103, scope and content of prior art are to be determined, differences between prior art and claims are to be ascertained, and level of ordinary skill in the pertinent art resolved; against this background, obviousness of subject matter is determined; such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to circumstances surrounding origin of subject matter sought to be patented; as indicia of obviousness, these inquiries may have relevancy.

9. Abandonment—Disclosure without claiming (§ 10.7)

Feature disclosed in patent drawings and specification, but not claimed therein, became public property.

10. Patentability—Tests of—In general (§ 51.701)

Patentability must be determined by consideration of subject matter sought to be patented taken as a whole.

11. Construction of specification and claims—By Patent Office proceedings—In general (§ 22.151)

Construction of specification and claims—By prior art (§ 22.20)

Construction of specification and claims—Claim defines invention (§ 22.30)

Invention is construed not only in light of claims, but also with reference to file wrapper or prosecution history in Patent Office; claims as allowed must be read and interpreted with reference to rejected ones and to state of prior art; claims that have been narrowed in order to obtain issuance of patent by distinguishing prior art cannot be sustained to cover that which was previously by limitation eliminated from patent.

12. Patentability — Evidence of — Commercial success—In general (§ 51.-4551)

Patentability—Evidence of—Delay and failure of others to produce invention (§ 51.459)

Legal inferences or subtests (long-felt need, commercial success) focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible to judicial treatment than are technical facts often present in patent litigation; they may aid judiciary and may serve to guard against slipping into hindsight and to resist temptation to read into prior art the teachings of invention in issue; however, they do not tip scales of patentability where differences from prior art were rendered apparent by prior patent before unsuccessful attempts to solve problem; it is irrelevant that no one chose to avail himself of knowledge stored in Patent Office and make a patent search.

Particular patents—Plow Clamp

2,627,798, Graham, Clamp for Vibrating Shank Plows, claims 1 and 2 invalid.
2,870,943, Scoggin, Pump-Type Liquid Sprayer Having Hold-down Cap, claims 1 and 2 invalid.

On writ of certiorari to Court of Appeals for the Eighth Circuit; 142 USPQ 243.

Action by William T. Graham and

Graham Plow, Inc., against John Deere Company of Kansas City and Deere & Company for patent infringement. On writ of certiorari to review judgment for defendants. Affirmed.

See also 137 USPQ 864, 144 USPQ 780.

ORVILLE O. GOLD (CLAUDE A. FISHBURN on the brief) both of Kansas City, Mo., for petitioners.

S. THOMAS MORRIS, Amarillo, Tex. (W. W. GIBSON, Amarillo, Tex., and THOMAS E. SCOFIELD, Kansas City, Mo., on the brief) for respondents.

STANTON T. LAWRENCE, JR., ROBERT E. ISNER, and CHARLES E. MCKENNEY, all of New York, N.Y., filed brief for New York Patent Law Association, amicus curiae.

J. VINCENT MARTIN, ALFRED H. EVANS, and RUSSELL E. SCHLORFF, all of Houston, Tex., filed brief for Patent, Trademark and Copyright Section of the State Bar of Texas, amicus curiae.

ROGER ROBB, Washington, D.C., filed brief for American Bar Association, amicus curiae.

E. ERNEST GOLDSTEIN and W. PAGE KEETON, both of Austin, Tex., filed brief amicus curiae.

GEORGE E. FROST and JAMES M. WETZEL, both of Chicago, Ill., filed brief for Illinois State Bar Association, amicus curiae.

On writs of certiorari to Court of Appeals for the Eighth Circuit; 142 USPQ 412.

Two actions against Cook Chemical Company for declaratory judgment of patent invalidity and noninfringement, one by Calmar, Inc., and one by Colgate-Palmolive Company, in which defendant counterclaims for patent infringement. On writs of certiorari to review judgments for defendant. Reversed.

See also 138 USPQ 432, 144 USPQ 780.

DENNIS G. LYONS, Washington, D.C. (VICTOR H. KRAMER, FRANCIS G. COLE, WATSON, COLE, GRINDLE & WATSON, and ARNOLD, FORTAS & PORTER, all of Washington, D.C., GEORGE H. MORTIMER, New York, N.Y., and HOWARD A. CRAWFORD, JACK W. R. HEADLEY, and LATHROP, RIGHTER, GORDON & PARKER, all of Kansas City, Mo., on the brief) for petitioners.

GORDON D. SCHMIDT, Kansas City, Mo. (HOVEY, SCHMIDT, JOHNSON & HOVEY, CARL E. ENGGAS, and WATSON, ESS, MARSHALL & ENGGAS, all of Kansas City, Mo., and HUGH B. COX and CHARLES A. MILLER, both of Washington, D.C., on the brief) for respondent.

MR. JUSTICE CLARK delivered the opinion of the Court.

After a lapse of 15 years, the Court again focuses its attention on the patentability of inventions under the standard of Art. I. § 8, cl. 8. of the Constitution and under the conditions prescribed by the laws of the United States. Since our last expression on patent validity, A. & P. Tea Co. v. Supermarket Corp., 340 U.S. 147, 87 USPQ 303 (1950), the Congress has for the first time expressly added a third statutory dimension to the two requirements of novelty and utility that had been the sole statutory test since the Patent Act of 1793. This is the test of obviousness, i.e., "whether the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made." Patent Act of 1952, 66 Stat. 798, 35 U.S.C. § 103 (1964 ed.).

[1] The questions, involved in each of the companion cases before us, are what effect did the 1952 Act have upon traditional statutory and judicial tests of patentability and what definitive tests are now required. We have concluded that the 1952 Act was intended to codify judicial precedents embracing the principle long ago announced by this Court in Hotchkiss v. Greenwood, 11 How. 248 (1850), and that, while the clear language of § 103 places emphasis on an inquiry into obviousness, the general level of innovation necessary to sustain patentability remains the same.

I.

The Cases

(a). No. 11, Graham v. John Deere Co., an infringement suit by petitioners, presents a conflict between two Circuits over the validity of a single patent on a "Clamp for vibrating Shank Plows." The invention, a combination of old mechanical elements, involves a device designed to absorb shock from plow shanks as they plow through rocky soil and thus to prevent damage to the plow. In 1955, the Fifth Circuit had held the patent valid under its rule that when a combination produces an "old result in a cheaper and otherwise more advantageous way," it is patentable. Jeoffroy Mfg., Inc. v. Graham, 219 F.2d 511, 104 USPQ 261, cert. denied, 350 U.S. 826, 107 USPQ 362. In 1964, the Eighth Circuit held, in the case at bar, that there was no new result in the patented combination and that the patent was,

therefore, not valid. 333 F.2d 529, 142 USPQ 243, reversing 216 F.Supp. 272, 137 USPQ 864. We granted certiorari, 379 U.S. 956, 144 USPQ 780. Although we have determined that neither Circuit applied the correct test, we conclude that the patent is invalid under § 103 and, therefore, we affirm the judgment of the Eighth Circuit.

(b). No. 37, Calmar, Inc. v. Cook Chemical Co., and No. 43, Colgate-Palmolive Co. v. Cook Chemical Co., both from the Eighth Circuit, were separate declaratory judgment actions, but were filed contemporaneously. Petitioner in Calmar is the manufacturer of a finger-operated sprayer with a "hold-down" cap of the type commonly seen on grocer's shelves inserted in bottles of insecticides and other liquids prior to shipment. Petitioner in Colgate-Palmolive is a purchaser of the sprayers and uses them in the distribution of its products. Each action sought a declaration of invalidity and noninfringement of a patent on similar sprayers issued to Cook Chemical as assignee of Baxter I. Scoggin, Jr., the inventor. By cross-action, Cook Chemical claimed infringement. The actions were consolidated for trial and the patent was sustained by the District Court. 220 F.Supp. 414, 138 USPQ 432. The Court of Appeals affirmed, 336 F.2d 110, 142 USPQ 412, and we granted certiorari, 380 U.S. 949. We reverse.

Manifestly, the validity of each of these patents turns on the facts. The basic problems, however, are the same in each case and require initially a discussion of the constitutional and statutory provisions covering the patentability of the inventions.

II.

[2] At the outset it must be remembered that the federal patent power stems from a specific constitutional provision which authorizes the Congress "To promote the Progress of * * * useful Arts, by securing for limited Times to * * * Inventors the exclusive Right to their * * * Discoveries * * *." Art. I, § 8.[1] The clause is both a grant of power and a limitation. This qualified authority, unlike the power often exercised in the Sixteenth and Seventeenth Centuries by the English Crown, is limited to the promotion of advances in the "useful arts." It was written against the backdrop of the practices—eventually curtailed by the Statute of Monopolies—of the Crown in granting monopolies to court favorites in goods or businesses which had long before been enjoyed by the public. See Meinhardt, Inventions, Patents and Monopoly, pp. 30-35 (London, 1946). The Congress in the exercise of the patent power may not overreach the restraints imposed by the stated constitutional purpose. Nor may it enlarge the patent monopoly without regard to the innovation, advancement or social benefit gained thereby. Moreover, Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available. Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must "promote the Progress of * * * useful Arts." This is the *standard* expressed in the Constitution and it may not be ignored. And it is in this light that patent "validity requires reference to a standard written into the Constitution." A. & P. Tea Co. v. Supermarket Corp., supra, at 154, 87 USPQ at 306.

Within the limits of the constitutional grant, the Congress may, of course, implement the stated purpose of the Framers by selecting the policy which in its judgment best effectuates the constitutional aim. This is but a corollary to the grant to Congress of any Article I power. Gibbons v. Ogden, 9 Wheat. 1. Within the scope established by the Constitution, Congress may set out conditions and tests for patentability. McClurg v. Kingsland, 1 How. 202, 206. It is the duty of the Commissioner of Patents and of the courts in the administration of the patent system to give effect to the constitutional standard by appropriate application, in each case, of the statutory scheme of the Congress.

Congress quickly responded to the bidding of the Constitution by enacting the Patent Act of 1790 during the second session of the First Congress. It created an agency in the Department of State headed by the Secretary of State, the Secretary of the Department of War and the Attorney General, any two of whom could issue a patent for a period not exceeding 14 years to any petitioner that "hath invented or discovered any useful art, manufacture, or device, or any improvement therein not before known or used" if the Board found that "the invention or discovery [was] sufficiently useful and important * * *." This group, whose members administered the patent system along with their

[1] The provision appears in the Constitution spliced together with the copyright provision, which we omit as not relevant here. See H.R. Rep. No. 1923, 82d Cong., 2d Sess., at 4 (1952); DeWolf, An Outline of Copyright Law, p. 15 (Boston 1925).

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other public duties, was known by its own designation as "Commissioners for the Production of the Useful Arts."

Thomas Jefferson, who as Secretary of State was a member of the group, was its moving spirit and might well be called the "First Administrator of our Patent System." See Federico, Operation of the Patent Act of 1790, 18 J. P. O. S. 237, 238 (1936). He was not only an administrator of the patent system under the 1790 Act, but was also the author of the 1793 Patent Act. In addition, Jefferson was himself an inventor of great note. His unpatented improvements on plows, to mention but one of his inventions, won acclaim and recognition on both sides of the Atlantic. Because of his active interest and influence in the early development of the patent system, Jefferson's views on the general nature of the limited patent monopoly under the Constitution, as well as his conclusions as to conditions for patentability under the statutory scheme, are worthy of note.

Jefferson, like other Americans, had an instinctive aversion to monopolies. It was a monopoly on tea that sparked the Revolution and Jefferson certainly did not favor an equivalent form of monopoly under the new government. His abhorrence of monopoly extended initially to patents as well. From France, he wrote to Madison urging a bill of rights provision restricting monopoly, and as against the argument that limited monopoly might serve to incite "ingenuity," he argued forcefully that "the benefit of even limited monopolies is too doubtful to be opposed to that of their general suppression," IV Writings of Thomas Jefferson (Ford ed.), at 476 (July 1788).

His views ripened, however, and in another letter to Madison after the adoption of the Bill of Rights, Jefferson stated that he would have been pleased by an express provision in this form:

> "Article 9. Monopolies may be allowed to persons for their own productions in literature, and their own inventions in the Arts, for a term not exceeding—years, but for no longer term and for no other purpose." Id., at 493 (Aug. 1789).

And he later wrote:

> "Certainly an inventor ought to be allowed a right to the benefit of his invention for some certain time * * *. Nobody wishes more than I do that ingenuity should receive liberal encouragement." Letter to Oliver Evans, V Writings of Thomas Jefferson, (Washington ed.), at 75 (1807).

Jefferson's philosophy on the nature and purpose of the patent monopoly is expressed in a letter to Isaac McPherson, a portion of which we set out in the margin.[2] He rejected a natural rights theory in intellectual property rights and clearly recognized the social and economic rationale of the patent system. The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge. The grant of an exclusive right to an invention was the creation of society—at odds with the inherent free nature of disclosed ideas—and was not to be freely given. Only inventions and discoveries which furthered human knowledge, and were new and useful, justified the special inducement of a limited private monopoly. Jefferson did not believe in granting patents for small details, obvious improvements, or frivolous devices. His writings evidence his insistance upon a high level of patentability.

As a member of the patent board for several years, Jefferson saw clearly the

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2 "Stable ownership is the gift of social law, and is given late in the progress of society. It would be curious, then, if an idea, the fugitive fermentation of an individual brain, could, of natural right, be claimed in exclusive and stable property. If nature has made any one thing less susceptible than all others of exclusive property, it is the action of the thinking power called an idea, which an individual may exclusively possess as long as he keeps it to himself; but the moment it is divulged, it forces itself into the possession of every one, and the receiver cannot dispossess himself of it. Its peculiar character, too, is that no one possesses the less, because every other possesses the whole of it. He who receives an idea from me, receives instruction himself without lessening mine; as he who lights his taper at mine, receives light without darkening mine. That ideas should freely spread from one to another over the globe, for the moral and mutual instruction of man, and improvement of his condition, seems to have been peculiarly and benevolently designed by nature. When she made them like fire, expansible over all space, without lessening their density in any point, and like the air in which we breathe, move, and have our physical being, incapable of confinement or exclusive appropriation. Inventions then cannot, in nature, be a subject of property. Society may give an exclusive right to the profits arising from them, as an encouragement to men to pursue ideas which may produce utility, but this may or may not be done according to the will and convenience of the society, without claim or complaint from anybody." VI Writings of Thomas Jefferson (Washington ed.), at 180 (1814).

difficulty in "drawing a line between things which are worth to the public the embarrassment of an exclusive patent and those which are not." The board on which he served sought to draw such a line and formulated several rules which are preserved in Jefferson's correspondence.[3] Despite the Board's efforts, Jefferson saw "with what slow progress a system of general rules could be matured." Because of the "abundance" of cases and the fact that the investigations occupied "more time of the members of the board than they could spare from their higher duties, the whole was turned over to the judiciary, to be matured into a system, under which everyone might know when his actions were safe and lawful." Letter to McPherson, supra, at 181. Apparently Congress agreed with Jefferson and the Board that the courts should develop additional, conditions for patentabillty. Although the Patent Act was amended, revised or codified some 50 times between 1790 and 1950, Congress steered clear of a statutory set of requirements other than the bare novelty and utility tests reformulated in Jefferson's draft of the 1793 Patent Act.

III.

[**3**] The difficulty of formulating conditions for patentability was heightened by the generality of the constitutional grant and the statutes implementing it, together with the underlying policy of the patent system that "the things which are worth to the public the embarrassment of an exclusive patent," as Jefferson put it, must outweigh the restrictive effect of the limited patent monopoly. The inherent problem was to develop some means of weeding out those inventions which would not be disclosed or devised but for the inducement of a patent.

This Court formulated a general condition of patentability in 1850 in Hotchkiss v. Greenwood, 11 How. 248. The patent involved a mere substitition of materials—porcelain or clay for wood or metal in door knobs—and the Court condemned it, holding: [4]

> "[U]nless more ingenuity and skill * * * were required than were possessed by an ordinary mechanic acquainted with the business, there was an absence of that degree of skill and ingenuity which constitute essential elements of every invention. In other words, the improvement is the work of a skilled mechanic, not that of the inventor." At p. 267.

Hotchkiss, by positing the condition that a patentable invention evidence more ingenuity and skill than that possessed by an ordinary mechanic acquainted with the business, merely distinguished between new and useful innovations that were capable of sustaining a patent and those that were not. The Hotchkiss test laid the cornerstone of the judicial evolution suggested by Jefferson and left to the courts by Congress. The language in the case, and in those which followed, gave birth to "invention" as a word of legal art signifying patentable inventions. Yet, as this Court has observed, "[t]he truth is the word ['invention'] cannot be defined in such a manner as to afford any substantial aid in determining whether a particular device involves an exercise of inventive faculty or not." McClain v. Ortmayer, 141 U.S. 419, 427 (1891), A. & P. Tea Co. v. Supermarket Corp., 340 U.S. at 151, 87 USPQ at 305. Its use as a label brought about a large variety of opinions as to its meaning both in the Patent Office, in the courts, and at the bar. The Hotchkiss formulation, however, lies not in any label, but in its functional approach to questions of patentability. In practice, Hotchkiss has required a comparison between the subject matter of the patent, or patent application, and the background skill of the calling. It has been from this comparison that patentability was in each case determined.

IV.

The 1952 Act.

[**4**] The Act sets out the conditions of patentability in three sections. An analysis of the structure of these three sections indicates that patentability is

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[3] "A machine of which we are possessed might be applied by every man to any use of which it is susceptible." Letter to Isaac McPherson, supra, at 181.

"A change of material should not give title to a patent. As the making a plowshare of cast rather than of wrought iron; a comb of iron instead of horn or ivory * * *." Ibid.

"A mere change of form should give no right to a patent, as a high quartered shoe instead of a low one; a round hat instead of a three square, or a square bucket instead of a round one." Id., at 182.

"[A combined use of old implements] A man has the right to use a saw, an axe, a plane separately; may he not combine their uses on the same piece of wood?" Letter to Oliver Evans, supra, at 298.

[4] In historical retrospect, the specific result in Hotchkiss flows directly from an application of one of the rules of the original board of "Commissioners," n. 3, second rule, supra.

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dependent upon three explicit conditions: novelty and utility as articulated and defined in § 101, and § 102, and nonobviousness, the new statutory formulation, as set out in § 103. The first two sections, which trace closely the 1874 codification, express the "new and useful" tests which have always existed in the statutory scheme and, for our purposes here, need no clarification.[5] The pivotal section around which the present controversy centers is § 103. It provides:

"§ 103. Conditions for patentability; non-obvious subject matter

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made."

The section is cast in relatively unambiguous terms. Patentability is to depend, in addition to novelty and utility, upon the "non-obvious" nature of the "subject matter sought to be patented" to a person having ordinary skill in the pertinent art.

The first sentence of this section is strongly reminiscent of the language in Hotchkiss. Both formulations place emphasis on the pertinent art existing at the time the invention was made and both are implicitly tied to advances in that art. The major distinction is that Congress has emphasized "non-obviousness" as the operative test of the section, rather than the less definite "invention" language of Hotchkiss that Congress thought had lead to "a large variety" of expressions in decisions and writings. In the title itself the Congress used the phrase "Conditions for patentability: *non-obvious subject matter*," thus focusing upon "non-obviousness" rather than "invention." [6] The Senate and House Reports, S. Rep. No. 1979, 82d Cong., 2d Sess. (1952); H. R. Rep. No. 1923, 82d Cong., 2d Sess. (1952), reflect this emphasis in these terms:.

"Section 103, for the first time in our statute, provides a condition which exists in the law and has existed for more than 100 years, but only by reason of decision of the Courts. An invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent. That has been expressed in a large variety of ways in decisions of the courts and in writings. Section 103 states this requirement in the title. It refers to the difference between the subject matter sought to be patented and the prior art, meaning

[5] "§ 101. Inventions patentable

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

"§ 102. Conditions for patentability; novelty and loss of right to patent

"A person shall be entitled to a patent unless—

"(a) The invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or

"(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, or

"(c) he has abandoned the invention, or

"(d) the invention was first patented or caused to be patented by the applicant or his legal representatives or assigns in a foreign country prior to the date of the application for patent in this country on an application filed more than twelve months before the filing of the application in the United States, or

"(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or

"(f) he did not himself invent the subject matter sought to be patented, or

"(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other."

The precursors of these sections are to be found in Act of February 21, 1793, c. 11, 1 Stat. 318; Act of July 4, 1836, c. 357, 5 Stat. 117; Act of July 8, 1870, c. 230, 16 Stat. 198; Rev. Stat. (1874) § 4886.

[6] The corresponding provision in the preliminary draft was titled "Conditions for Patentability; *lack of invention*," Proposed Revision and Amendment of the Patent Laws, Preliminary Draft with Notes of House Committee on the Judiciary (Committee Print, 1950).

what was known before as described in section 102. If this difference is such that the subject matter as a whole would have been obvious at the time to a person skilled in the art, then the subject matter cannot be patented.

"That provision paraphrases language which has often been used in decisions of the courts, and the section is added to the statute for uniformity and definiteness. This section should have a stabilizing effect and minimize great departures which have appeared in some cases." H. R. Rep., at 7; S. Rep., at 6.

[5] It is undisputed that this section was, for the first time, a statutory expression of an additional requirement for patentability, originally expressed in Hotchkiss. It also seems apparent that Congress intended by the last sentence of § 103 to abolish the test it believed this Court announced in the controversial phrase "flash of genius," used in Cuno Corp. v. Automatic Devices Corp., 314 U.S. 84, 51 USPQ 272 (1941).[7]

It is contended, however, by some of the parties and by several of the amici that the first sentence of § 103 was intended to sweep away judicial precedents and to lower the level of patentability. Others contend that the Congress intended to codify the essential purpose reflected in existing judicial precedents—the rejection of insignificant variations and innovations of a commonplace sort—and also to focus inquiries under § 103 upon nonobviousness, rather than upon "invention," as a means of achieving more stability and predictability in determining patentability and validity.

The Reviser's Note to this section,[8] with apparent reference to Hotchkiss, recognizes that judicial requirements as to "lack of patentable novelty have been followed since at least as early as 1850." The note indicates that the section was inserted because it "may have some stabilizing effect and also serve as a basis for the addition at a later time of criteria which may be worked out." To this same effect are the reports of both Houses, supra, which state that the first sentence of the section "paraphrases the language which has often been used in decisions of the courts and the section is added to the statute for unformity and definitiveness."

[6] We believe that this legislative history, as well as other sources,[9] show that the revision was not intended by Congress to change the general level of patentable invention. We conclude that the section was intended merely as a codification of judicial precedents embracing the Hotchkiss condition, with congressional directions that inquiries into the obviousness of the subject matter sought to be patented are a prerequisite to patentability.

V.

[7] Approached in this light, the § 103 additional condition, when fol-

[7] The sentence in which the phrase occurs reads: "The new device, however useful it may be, must reveal the flash of creative genius, not merely the skill of the calling." At p. 91, 51 USPQ at 275. Although some writers and lower courts found in the language connotations as to the frame of mind of the inventors, none were so intended. The opinion approved Hotchkiss specifically, and the reference to "flash of creative genius" was but a rhetorical embellishment of language going back to 1833. Cf. "exercise of genius," Shaw v. Cooper, 7 Pet. 292; "inventive genius," Rickendorfer v. Farber, 92 U.S. 347 (1875); Concrete Appliance Products Co.; "flash of thought," Densmore v. Scofield, 102 U.S. 375 (1880); "intuitive genius," C. A. Potts Co. v. Creager, 155 U.S. 597 (1895). Rather than a more exacting standard, Cuno merely rhetorically restated the requirement that the subject matter sought to be patented must be beyond the skill of the calling. It was the device, not the invention, that had to reveal the "flash of creative genius." See Boyajian, The Flash of Creative Genius, 25 J.P.O.S. 776, 780, 781 (1943); Pacific Contact Laboratories, Inc. v. Solex Laboratories, Inc., 209 F.2d 529, 533, 100 USPQ 12, 14; Brown & Sharpe Mfg. Co., v. Kar Engineering Co., 154 F.2d 48, 51-52, 68 USPQ 427, 430; In re Shortell, 142 F.2d 292, 295-296, 61 USPQ 362, 366-367.

[8] "There is no provision corresponding to the first sentence explicitly stated in the present statutes, but the refusal of patents by the Patent Office, and the holding of patents invalid by the courts, on the ground of lack of invention or lack of patentable novelty has been followed since at least as early as 1850. This paragraph is added with the view that an explicit statement in the statute may have some stabilizing effect, and also to serve as a basis for the addition at a later time of some criteria which may be worked out.

"The second sentence states that patentability as to this requirement is not to be negatived by the manner in which the invention was made, that is, it is immaterial whether it resulted from long toil and experimentation or from a flash of genius."

[9] See Efforts to Establish a Statutory Standard of Invention, Study No. 7, Senate Subcommittee on Patents, Trademarks and Copyrights, 85th Cong., 2d Sess. (Committee Print, 1961); Hearings, Subcommittee No. 3, House Committee on the Judiciary, on H.R. 3760, 82d Cong., 1st Sess. (1951).

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lowed realistically, will permit a more practical test of patentability. The emphasis on nonobviousness is one of inquiry, not quality and, as such, comports with the constitutional strictures.

[8] While the ultimate question of patent validity is one of law, A. & P. Tea Co. v. Supermarket Corp., supra, at 155, 87 USPQ at 307, the § 103 condition, which is but one of three conditions, each of which must be satisfied, lends itself to several basic factual inquiries. Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy. See Note, Subtests of "Nonobviousness," 112 U. Pa. L. Rev. 1169 (1964).

This is not to say, however, that there will not be difficulties in applying the nonobviousness test. What is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context. The difficulties, however, are comparable to those encountered daily by the courts in such frames of reference as negligence and scienter, and should be amenable to a case-by-case development. We believe that strict observance of the requirements laid down here will result in that uniformity and definitiveness which Congress called for in the 1952 Act.

While we have focused attention on the appropriate standard to be applied by the courts, it must be remembered that the primary responsibility for sifting out unpatentable material lies in the Patent Office. To await litigation is—for all practical purposes—to debilitate the patent system. We have observed a notorious difference between the standards applied by the Patent Office and by the courts. While many reasons can be adduced to explain the discrepancy, one may well be the free rein often exercised by examiners in their use of the concept of "invention." In this connection we note that the Patent Office is confronted with a most difficult task. Almost 100,000 applications for patents are filed each year. Of these, about 50,000 are granted with the result that the backlog now runs well over 200,000. United States Patent Office, Index of Patents, p. 1123 (1963). This is itself a compelling reason for the Commissioner to strictly adhere to the 1952 Act as interpreted here. This would we believe, not only expedite disposition but bring about a closer concurrence between administrative and judicial precedent.[10]

Although we conclude here that the inquiry which the Patent Office and the courts must make as to patentability must be beamed with greater intensity on the requirements of § 103, it bears repeating that we find no change in the general strictness with which the overall test is to be applied. We have been urged to find in § 103 a relaxed standard, supposedly a congressional reaction to the "increased standard" applied by this Court in its decisions over the last 20 or 30 years. The standard has remained invariable in this Court. Technology, however, has advanced—and with remarkable rapidity in the last 50 years. Moreover the ambit of applicable art in given fields of science has widened by disciplines unheard of a half-century ago. It is but an evenhanded application to require those persons granted the benefit of a patent monopoly be charged with an awareness of these changed conditions. The same is true of the less technical, but still useful arts. He who seeks to build a better mousetrap today has a long path to tread before reaching the Patent Office.

VI.

We now turn to the application of the conditions found necessary for patentability to the cases involved here:

A. The patent in issue in No. 11, Graham v. John Deere Co.

This patent, No. 2,627,798 (hereinafter called the '798 patent) relates to a spring clamp which permits plow shanks to be pushed upward when they hit obstructions in the soil, and then springs the shanks back into normal position when the obstruction is passed over. The device, which we show diagrammatically in the accompanying sketches (Appendix, Fig. 1), is fixed to the plow frame as a unit. The mechanism around which the controversy centers is basically a hinge. The top

[10] The President has appointed a Commission on the Patent System. Executive Order No. 11215, 30 Fed. Reg. 4661 (April 10, 1965). It is hoped that its studies may develop more efficient administrative procedures and techniques that will further expedite dispositions and at the same time insure the strict application of appropriate tests of patentability.

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half of it, known as the upper plate (marked 1 in the sketches), is a heavy metal piece clamped to the plow frame (2) and is stationary relative to the plow frame. The lower half of the hinge, known as the hinge plate (3), is connected to the rear of the upper plate by a hinge pin (4) and rotates downward with respect to it. The shank (5), which is bolted to the forward end of the hinge plate (at 6), runs beneath the plate and parallel to it for about nine inches, passes through a stirrup (7), and then continues backward for several feet curving down toward the ground. The chisel (8), which does the actual plowing, is attached to the rear end of the shank. As the plow frame is pulled forward, the chisel rips through the soil, thereby plowing it. In the normal position, the hinge plate and the shank are kept tight against the upper plate by a spring (9), which is atop the upper plate. A rod (10) runs through the center of the spring, extending down through holes in both plates and the shank. Its upper end is bolted to the top of the spring while its lower end is hooked against the underside of the shank.

When the chisel hits a rock or other obstruction in the soil, the obstruction forces the chisel and the rear portion of the shank to move upward. The shank is pivoted (at 11) against the rear of the hinge plate and pries open the hinge against the closing tendency of the spring. (See sketch labeled "Open Position," Appendix, Fig. 1.). This closing tendency is caused by the fact that, as the hinge is opened, the connecting rod is pulled downward and the spring is compressed. When the obstruction is passed over, the upward force on the chisel disappears and the spring pulls the shank and hinge plate back into their original position. The lower, rear portion of the hinge plate is constructed in the form of a stirrup (6) which brackets the shank, passing around and beneath it. The shank fits loosely into the stirrup (permitting a slight up and down play). The stirrup is designed to prevent the shank from recoiling away from the hinge plate, and thus prevents excessive strain on the shank near its bolted connection. The stirrup also girds the shank, preventing it from fishtailing from side to side.

In practical use, a number of spring-hinge-shank combinations are clamped to a plow frame, forming a set of ground-working chisels capable of withstanding the shock of rocks and other obstructions in the soil without breaking the shanks.

Background of the Patent.

Chisel plows, as they are called, were developed for plowing in areas where the ground is relatively free from rocks or stones. Originally, the shanks were rigidly attached to the plow frames. When such plows were used in the rocky glacial soils of some of the Northern States, they were found to have serious defects. As the chisels hit buried rocks, a vibratory motion was set up and tremendous forces were transmitted to the shank near its connection to the frame. The shanks would break. Graham, one of the petitioners, sought to meet that problem, and in 1950 obtained a patent, U.S. No. 2,493,811, on a spring clamp which solved some of the difficulties. Graham and his companies manufactured and sold the '811 clamps. In 1950, Graham modified the '811 structure and filed for a patent. That patent, the one in issue, was granted in 1953. This suit against competing plow manufacturers resulted from charges by petitioners that several of respondents' devices infringed the '798 patent.

The Prior Art.

Five prior patents indicating the state of the art were cited by the Patent Office in the prosecution of the '798 application. Four of these patents, 10 other United States patents and two prior use spring clamp arrangements not of record in the '798 file wrapper were relied upon by respondent as revealing the prior art. The District Court and the Court of Appeals found that the prior art "as a whole in one form or another contains all of the mechanical elements of the '798 Patent." One of the prior use clamp devices not before the Patent Examiner—Glencoe—was found to have "all of the elements."

We confine our discussion to the prior patent of Graham, '811, and to the Glencoe clamp device, both among the references asserted by respondents. The Graham '811 and '798 patent devices are similar in all elements, save two; (1) the stirrup and the bolted connection of the shank to the hinge plate do not appear in '811; and (2) the position of the shank is reversed, being placed in patent '811 above the hinge plate, sandwiched between it and the upper plate. The shank is held in place by the spring rod which is hooked against the bottom of the hinge plate passing through a slot in the shank. Other differences are of no consequence to our examination. In practice the '811 patent arrangement permitted the shank to wobble or fishtail because it was not rigidly fixed to the hinge plate; moreover, as the hinge plate was below the

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shank, the latter caused wear on the upper plate, a member difficult to repair or replace.

Graham's '798 patent application contained 12 claims. All were rejected as not distinguished from the Graham '811 patent. The inverted relationship of the shank was specifically rejected as was the bolting of the shank to the hinge plate. The Patent Office examiner found these to be "matters of design well within the expected skill of the art and devoid of invention." Graham withdrew the original claims and substituted the two new ones which are substantially those in issue here. His contention was that wear was reduced in patent '798 between the shank and the heel or rear of the upper plate.[11] He also emphasized several new features, the relevant one here being that the bolt used to connect the hinge plate and shank maintained the upper face of the shank in continuing and constant contact with the underface of the hinge plate.

Graham did not urge before the Patent Office the greater "flexing" qualities of the '798 patent arrangement which he so heavily relied on in the courts. The sole element in patent '798 which petitioners argue before us is the interchanging of the shank and hinge plate and the consequences flowing from this arrangement. The contention is that this arrangement — which petitioners claim is not disclosed in the prior art— permits the shank to flex under stress for its *entire* length. As we have sketched (see sketch, "Graham '798 Patent" in Appendix, Fig. 2), when the chisel hits an obstruction the resultant force (A) pushes the rear of the shank upward and the shank pivots at the underface of the upper plate at its rear (C). The natural tendency is for that portion of the shank between the pivot point and the bolted connection (i.e., between C and D) to bow downward and away from the hinge plate. The maximum distance (B) that the shank moves away from the plate is slight — for emphasis, greatly exaggerated in the sketches. This is so because of the strength of shank and the short—nine inches or so —length of that portion of the shank between (C) and (D). On the contrary, in patent '811 (see sketch, "Graham '811 Patent" in Appendix, Fig. 2), the pivot points is the upper plate at point (c); and while the tendency for the shank to bow between points (c) and (d) is the same as in '798, the shank is restricted because of the underlying hinge and cannot flex as freely. In practical effect, the shank flexes only between points (a) and (c), and not along the entire length of the shank, as in '798. Petitioners say that this difference in flex, though small, effectively absorbs the tremendous forces of the shock of obstructions whereas prior art arrangements failed.

The Obviousness of the Differences.

We cannot agree with petitioners. We assume that the prior art does not disclose such an arrangement as petitioners claim in patent '798. Still we do not believe that the argument on which petitioners' contention is bottomed supports the validity of the patent. The tendency of the shank to flex is the same in all cases. If free-flexing, as petitioners now argue, is the crucial difference above the prior art, then it appears evident that the desired result would be obtainable by not boxing the shank within the confines of the hinge.[12] The only other effective place available in the arrangement was to attach it below the hinge plate and run it through a stirrup or bracket that would not disturb its flexing qualities. Certainly a person having ordinary skill in the prior art, given the fact that the flex in the shank could be utilized more effectively if allowed to run the entire length of the shank, would immediately see that the thing to do was what Graham did, i.e., invert the shank and the hinge plate.

Petitioners' argument basing validity on the free-flex theory raised for the first time on appeal is reminiscent of Lincoln Engineering Co. v. Stewart-Warner Corp., 303 U.S. 545, 37 USPQ 1, 3 (1938), where the Court called such

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[11] In '811, where the shank was above the hinge plate, an upward movement of the chisel forced the shank up against the underside of the rear of the upper plate. The upper plate thus acted as the fulcrum about which the hinge was pried open. Because of this, as well as the location of the hinge pin, the shank rubbed against the heel of the upper plate causing wear both to the plate and to the shank. By relocating the hinge pin and by placing the hinge plate between the shank and the upper plate, as in 798, the rubbing was eliminated and the wear point was changed to the hinge plate, a member more easily removed or replaced for repair.

[12] Even petitioners' expert testified to that effect:

"Q. Given the same length of the forward portion of the clamp * * * you would anticipate that the magnitude of flex [in 798] would be precisely the same or substantially the same as in 811, wouldn't you?

"A. I would think so."

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an effort "an afterthought. No such function * * * is hinted at in the specifications of the patent. If this were so vital an element in the functioning of the apparatus it is strange that all mention of it was omitted." At p. 550, 37 USPQ at 3. No "flexing" argument was raised in the Patent Office. Indeed, the trial judge specifically found that "flexing is not a claim of the patent in suit * * *" and would not permit interrogation as to flexing in the accused devices. Moreover, the clear testimony of petitioners' experts shows that the flexible advantages flowing from the '798 arrangement are not, in fact, a significant feature in the patent.[13]

We find no nonobious facets in the '798 arrangement. The wear and repair claims were sufficient to overcome the patent examiner's original conclusions as to the validity of the patent. However, some of the prior art, notably Glencoe, was not before him. There the hinge plate is below the shank but, as the courts below found, all of the elements in the '798 patent are present in the Glencoe structure. Furthermore, even though the position of the shank and hinge plate appears reversed in Glencoe, the mechanical operation is identical. The shank there pivots about the underside of the stirrup, which in Glencoe is *above* the shank. In other words, the stirrup in Glencoe serves exactly the same function as the heel of the hinge plate in '798. The mere shifting of the wear point to the heel of the '798 hinge plate from the stirrup of Glencoe—itself a part of the hinge plate—presents no operative mechanical distinctions, much less nonobvious differences.

B. The Patent in issue in No. 37, Calmar, Inc. v. Cook Chemical Co. and in No. 43, Colgate Palmolive Co. v. Cook Chemical Co.

The single patent[14] involved in these cases relates to a plastic finger sprayer with a "hold down" lid used as a built-in dispenser for containers or bottles packaging liquid products, principally household insecticides. Only the first two of the four claims in the patent are involved here and we, therefore, limit our discussion to them. We do not set out those claims here since they are printed in 220 F.Supp., at pp. 417-418, 138 USPQ at 435.

In essence the device here combines a finger-operated pump sprayer, mounted in a container or bottle by means of a container cap, with a plastic overcap which screws over the top of and depresses the sprayer (see Figure 3 in the Appendix). The pump sprayer passes through the container cap and extends down into the liquid in the container; the overcap fits over the pump sprayer and screws down on the outside of the collar mounting or retainer which is molded around the body of the sprayer. When the overcap is screwed down on this collar mounting a seal is formed by the engagement of a circular ridge or rib located above the threads on the collar mounting with a mating shoulder located inside the overcap above its threads.[15] The overcap, as it is screwed down, depresses the pump plunger rendering the pump inoperable and when the seal is effected, any liquid which might seep into the overcap through or around the pump is prevented from leaking out of the overcap. The overcap serves also to protect the sprayer head and prevent damage to it during shipment or merchandising. When the overcap is in place it does not reach the cap of the container or bottle and in no way engages it since a slight space is left between those two pieces.

The device, called a shipper-sprayer in the industry, is sold as an integrated unit with the overcap in place enabling the insecticide manufacturer to install it on the container or bottle of liquid in a single operation in an automated bottling process. The ultimate consumer simply unscrews and discards the overcap, the pump plunger springs up and the sprayer is ready for use.

The Background of the Patent.

For many years manufacturers engaged in the insecticide business had

[13] "Q. * * * Do you regard the small degree of flex in the forward end of the shank that lies between the pivot point and the point of spring attachment to be of any significance or any importance to the functioning of a device such as 798? A. Unless you are approaching the elastic limit, I think this flexing will reduce the maximum stress at the point of pivot there, where the maximum stress does occur. I think it will reduce that. I don't know how much.

"Q. Do you think it is a substantial factor, a factor of importance in the functioning of the structure? A. Not a great factor, no."

The same expert previously testified similarly in Jeoffroy, supra.

[14] The patent is U.S. No. 2,870,943 issued in 1959 to Cook Chemical Co. as assignee of Burton I. Scoggin, Jr., the inventor. In No. 37 Calmar is the manufacturer of an alleged infringing device, and, in No. 43, Colgate is a purchaser of Calmar and user of its device.

[15] Our discussion here relates to the overcap seal. The container itself is sealed in the customary way through the use of a container gasket located between the container and the container cap.

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faced a serious problem in developing sprayers that could be integrated with the containers or bottles in which the insecticides were marketed. Originally, insecticides were applied through the use of tin sprayers, not supplied by the manufacturer. In 1947, Cook Chemical, an insecticide manufacturer, began to furnish its customers with plastic pump dispensers purchased from Calmar. The dispenser was an unpatented finger-operated device mounted in a perforated cardboard holder and hung over the neck of the bottle or container. It was necessary for the ultimate consumer to remove the cap of the container and insert and attach the sprayer to the latter for use.

Hanging the sprayer on the side of the container or bottle was both expensive and troublesome. Packaging for shipment had to be a hand operation, and breakage and pilferage as well as the loss of the sprayer during shipment and retail display often occurred. Cook Chemical urged Calmar to develop an integrated sprayer that could be mounted directly in a container or bottle during the automated filling process and that would not leak during shipment or retail handling. Calmar did develop some such devices but for various reasons they were not completely successful. The situation was aggravated in 1954 by the entry of Colgate-Palmolive into the insecticide trade with its product marketed in aerosol spray cans. These containers, which used compressed gas as a propellent to dispense the liquid, did not require pump sprayers.

During the same year Calmar was acquired by the Drackett Company. Cook Chemical became apprehensive of its source of supply for pump sprayers and decided to manufacture its own through a subsidiary, Bakan Plastics, Inc. Initially, it copied its design from the unpatented Calmar sprayer, but an officer of Cook Chemical, Scoggin, was assigned to develop a more efficient device. By 1956 Scoggin had perfected the shipper-sprayer in suit and a patent was granted in 1959 to Cook Chemical as his assignee. In the interim Cook Chemical began to use Scoggin's device and it was also marketed to the trade. The device was well received and soon became widely used.

In the meanwhile, Calmar employed two engineers, Corsett and Cooprider, to perfect a shipper-sprayer and by 1958 it began to market its SS-40, a device very much similar to Scoggin's. When the Scoggin patent issued, Cook Chemical charged Calmar's SS-40 with infringement and this suit followed.

The Opinions of the District Court and the Court of Appeals.

At the outset it is well to point up that the parties have always disagreed as to the scope and definition of the invention claimed in the patent in suit. Cook Chemical contends that the invention encompasses a unique combination of admittedly old elements and that patentability is found in the result produced. Its expert testified that the invention was "the first commercially successful, inexpensive, integrated shipping closure pump unit which permitted automated assembly with a container of household insecticide or similar liquids to produce a practical ready-to-use package which should be shipped without external leakage and which was so organized that the pump unit with its hold-down cap could be itself assembled and sealed and then later assembled and sealed on the container without breaking the first seal." Cook Chemical stresses the long-felt need in the industry for such a device; the inability of others to produce it; and its commercial success—all of which, contends Cook, evidences the nonobvious nature of the device at the time it was developed. On the other hand, Calmar says that the differences between Scoggin's shipper-sprayer and the prior art relate only to the design of the overcap and that the differences are so inconsequential that the device as a whole would have been obvious at the time of its invention to a person having ordinary skill in the art.

Both courts accepted Cook Chemical's contentions. While the exact basis of the District Court's holding is uncertain, it did find the subject matter of the patent new, useful and nonobvious. It concluded that Scoggin "had produced a sealed and protected sprayer unit which the manufacturer need only screw onto the top of its container much in the same fashion as a simple cap." 220 F.Supp. at 418, 138 USPQ at 436. Its decision seems to be bottomed on the finding that the Scoggin sprayer solved the long-standing problem that had confronted the industry.[16] The Court of Appeals also found validity in the

[16] "By the same reasoning, may it not also be said that if [the device] solved a long-sought need, it was likewise novel? If it meets the requirements of being new, novel, and useful, it was the subject of invention, although it may have been a short step, nevertheless it was the last step that ended the journey. The last step is the one that wins and he who takes it when others could not, is entitled to patent protection." 220 F.Supp. at 421, 138 USPQ at 438.

"novel 'marriage' of the sprayer with the insecticide container" which took years in discovery and in "the immediate commercial success" which it enjoyed. While finding that the individual elements of the invention were "not novel per se" the court found "nothing in the prior art suggesting Scoggin's unique combination of these old features as would solve the problem * * * which for fears besat the insecticide industry." It concluded that "the * * * [device] * * * meets the exacting standard required for a combination of old elements to rise to the level of patentable invention by fulfilling the long-felt need with an economical, efficient, utilitarian apparatus which achieved novel results and immediate commercial success." 336 F.2d at 114, 142 USPQ at 415.

The Prior Art.

Only two of the five prior art patents cited by the Patent Office Examiner in the prosecution of Scoggin's application are necessary to our discussion, i.e., Lohse U.S. Patent No. 2,119,884 (1938) and Mellon U.S. Patent No. 2,586,687 (1952). Others are cited by Calmar that were not before the examiner, but of these our purposes require discussion only of the Livingstone U.S. Patent No. 2,751,480 (1953). Simplified drawings of each of these patents are reproduced in the Appendix, Figs. 4—6 for comparison and description.

The Lohse patent (Fig. 4) is a shipper-sprayer designed to perform the same function as Scroggin's device. The differences, recognized by the District Court, are found in the overcap seal which in Lohse is formed by the skirt of the overcap engaging a washer or gasket which rests upon the upper surface of the container cap. The court emphasized that in Lohse "there are no seals above the threads and below the sprayer head." 220 F.Supp. at 419—420, 138 USPQ at 437.

The Mellon patent (Fig. 5), however, discloses the idea of effecting a seal above the threads of the overcap. Mellon's device, likewise a shipper-sprayer, differs from Scoggin's in that its overcap screws directly on the container, and a gasket, rather than a rib, is used to effect the seal.

Finally, Livingstone (Fig. 6) shows a seal above the threads accomplished without the use of a gasket or washer.[17] Although Livingstone's arrangement was designed to cover and protect pouring spouts, his sealing feature is strikingly similar to Scoggin's. Livingstone uses a tongue and groove technique in which the tongue, located on the upper surface of the collar, fits into a groove on the inside of the overcap. Scoggin employed the rib and shoulder seal in the identical position and with less efficiency because the Livingstone technique is inherently a more stable structure, forming an interlock that withstands distortion of the overcap when subjected to rough handling. Indeed, Cook Chemical has now incorporated the Livingstone closure into its own shipper-sprayers as had Calmar in its SS—40.

The Invalidity of the Patent.

[**10**] Let us first return to the fundamental disagreement between the parties. Cook Chemical, as we noted at the outset, urges that the invention must be viewed as the overall combination, or—putting it in the language of the statute—that we must consider the subject matter sought to be patented taken as a whole. With this position, taken in the abstract there is of course no quibble. But the history of the prosecution of the Scoggin application in the Patent Office reveals a substantial divergence in respondent's present position.

As originally submitted, the Scoggin application contained 15 claims which in very broad terms claimed the entire combination of spray pump and overcap. No mention of, or claim for, the sealing features were made. All 15 claims were rejected by the examiner because (1) the applicant was vague and indefinite as to what the invention was, and (2) the claims were met by Lohse. Scoggin canceled these claims and submitted new ones. Upon a further series of rejections and new submissions, the Patent Office Examiner, after an office interview, at last relented. It is crystal-clear that after the first rejection, Scoggin relied entirely upon the sealing arrangement as the exclusive patentable difference in his combination. It is likewise clear that it was on that feature that the examiner allowed the claims. In fact, in a letter accompanying the final submission of claims, Scoggin, through his attorney, stated that "agreement was reached between the Honorable Examiner and applicant's attorney relative to *limitations* which must be in the claims in order to define novelty over the previously applied disclosure of

[**9**] [17] While the sealing feature was not specifically claimed in the Livingstone patent, it was disclosed in the drawings and specifications. Under long-settled law the feature became public property. Miller v. Brass Company, 104 U.S. 350, 352 (1881).

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Lohse when considered in view of the newly cited patents of Mellon and Darley, Jr." (Italics added.)

Moreover, those limitations were specifically spelled out as (1) the use of a rib seal and (2) an overcap whose lower edge did not contact the container cap. Mellon was distinguished, as was the Darley patent, infra, n. 18, on the basis that although it disclosed a hold-down cap with a seal located above the threads, it did not disclose a rib seal disposed in such position as to cause the lower peripheral edge of the overcap "to be maintained out of contacting relationship with [the container] cap * * * when * * * [the overcap] was screwed [on] tightly * * *." Scoggin maintained that the "obvious modification" of Lohse in view of Mellon would be merely to place the Lohse gasket above the threads with the lower edge of the overcap remaining in tight contact with the container cap or neck of the container itself. In other words, the Scoggin invention was limited to the use of a rib—rather than a washer or gasket—and the existence of a slight space between the overcap and the container cap.

[11] It is, of course, well-settled that an invention is construed not only in the light of the claims, but also with reference to the file wrapper or prosecution history in the Patent Office. Hogg v. Emerson, 11 How. 587 (1850); Crawford v. Heysinger, 123 U.S. 589 (1887). Claims as allowed must be read and interpreted with reference to rejected ones and to the state of the prior art; and claims that have been narrowed in order to obtain the issuance of a patent by distinguishing the prior art cannot be sustained to cover that which was previously by limitation eliminated from the patent. Powers-Kennedy Co. v. Concrete Co., 282 U.S. 175, 185-186, 7 USPQ 122, 126 (1930); Schriber Co. v. Cleveland Trust Co., 311 U.S. 211, 220-221, 47 USPQ 345, 348-349 (1940).

Here, the patentee obtained his patent only by accepting the limitations imposed by the examiner. The claims were carefully drafted to reflect these limitations and Cook Chemical is not now free to assert a broader view of Scoggin's invention. The subject matter as a whole reduces, then, to the distinguishing features clearly incorporated into the claims. We now turn to those features.

As to the space between the skirt of the overcap and the container cap, the District Court found:

"Certainly without a space so described there could be no inner seal with the cap, but such a space is not new or novel, it is necessary to the formation of the seal within the hold-down cap.

"*To me this language is descriptive of an element of the patent, but not a part of the invention.* It is too simple, really, to require much discussion. In this device the hold-down cap was intended to perform two functions—to hold down the sprayer head and to form a solid tight seal between the shoulder and the collar below. In assembling the element it is necessary to provide this space in order to form the seal." 220 F.Supp at 420, 138 USPQ at 437. (Italics added.)

The court correctly viewed the significance of the feature. We are at a loss to explain the examiner's allowance on the basis of such a distinction. Scoggin was able to convince the examiner that Mellon's cap contacted the bottle neck while his did not. Although the drawings included in the Mellon application show that the cap might touch the neck of the bottle when fully screwed down, there is nothing—absolutely nothing—which indicates that the cap was designed at any time to *engage* the bottle neck. It is palpably evident that Mellon embodies a seal formed by a gasket compressed between the cap and the bottle neck. It follows that the cap in Mellon will not seal if it does not bear down on the gasket and this would be impractical, if not impossible, under the construction urged by Scoggin before the examiner. Moreover, the space so strongly asserted by Cook Chemical appears quite plainly on the Livingstone device, a reference not cited by the examiner.

The substitution of a rib built into a collar likewise presents no patentable difference above the prior art. It was fully disclosed and dedicated to the public in the Livingstone patent. Cook Chemical argues, however, that Livingstone is not in the *pertinent* prior art because it relates to liquid containers having pouring spouts rather than pump sprayers. Apart from the fact that respondent made no such objection to similar references cited by the examiner,[18] so restricted a view of the applicable prior art is not justified. The problems confronting Scoggin and the insecticide

[18] In addition to Livingstone and Mellon, the examiner cited Slade, U.S. Patent No. 2,844,290 (hold-down cap for detergent cans having a pouring spout); Nilson, U.S. Patent No. 2,118,222 (combined cap and spout for liquid dispensing containers); Darley, Jr., U.S. Patent No. 1,447,712 (containers for toothpaste, cold creams and other semi-liquid substances).

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industry were not insecticide problems; they were mechanical closure problems. Closure devices in such a closely related art as pouring spouts for liquid containers are at the very least pertinent references. See, II Walker, Patents § 260 (Deller ed. 1937).

[12] Cook Chemical insists, however, that the development of a workable shipper-sprayer eluded Calmar, who had long and unsuccessfully sought to solve the problem. And, further, that the long-felt need in the industry for a device such as Scoggin's together with its wide commercial success supports its patentability. These legal inferences or subtests do focus attention on economic and motivational rather than technical issues and are, therefore, more susceptible to judicial treatment than are the highly technical facts often present in patent litigation. See Learned Hand in Reiner v. I. Leon Co., 285 F.2d 501, 504, 128 USPQ 25, 27-28, cert. den. 366 U.S. 929, 129 USPQ 502 (1960). See also Comment, Subtests of "Nonobviousness." 112 Pa. L.Rev. 1169 (June 1964). Such inquiries may lend a helping hand to the judiciary which, as Mr. Justice Frankfurter observed, is most ill-fitted to discharge the technological duties cast upon it by patent legislation. Marconi Wireless Co. v. United States, 320 U.S. 1, 60, 57 USPQ 471, 496 (1943). They may also serve to "guard against slipping into hindsight," Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co., 332 F.2d 406, 412, 141 USPQ 549, 555 (1964), cert. denied 379 U.S. 888, 143 USPQ 465, and to resist the temptation to read into the prior art the teachings of the invention in issue.

However, these factors do not, in the circumstances of this case, tip the scales of patentability. The Scoggin invention, as limited by the Patent Office and accepted by Scoggin, rests upon exceedingly small and quite nontechnical mechanical differences in a device which was old in the art. At the latest, those differences were rendered apparent in 1953 by the appearance of the Livingstone patent, and unsuccessful attempts to reach a solution to the problems confronting Scoggin made before that time because wholly irrelevant. It is also irrelevant that no one apparently chose to avail themselves of knowledge stored in the Patent Office and readily available by the simple expedient of conducting a patent search—a prudent and nowdays common preliminary to well organized research. Mast, Foos & Co. v. Stover Mfg. Co., 177 U.S. 485 (1900). To us, the limited claims of the Scoggin patent are clearly evident from the prior art as it stood at the time of the invention.

We conclude that the claims in issue in the Scoggin patent must fall as not meeting the test of § 103, since the differences between them and the pertinent prior art would have been obvious to a person reasonably skilled in that art.

The judgment of the Court of Appeals in No. 11 is affirmed. The judgment of the Court of Appeals in Nos. 37 and 43 is reversed and the cases remanded to the District Court for disposition not inconsistent with this opinion.

It is so ordered

MR. JUSTICE STEWART took no part in the consideration or decision of Nos. 37 and 43.

MR. JUSTICE FORTAS took no part in the consideration or decision of these cases.

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Figure 1.—GRAHAM '798 PATENT

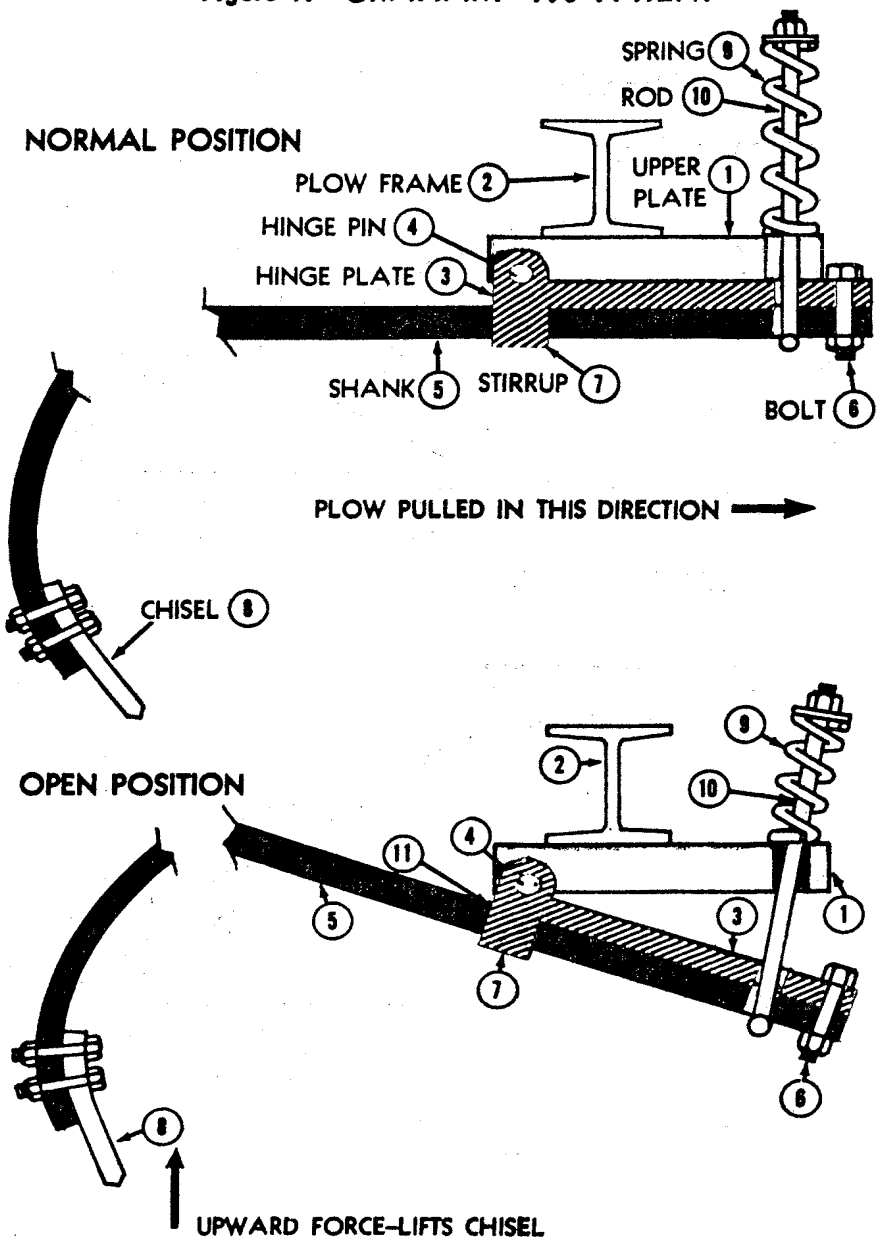

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Figure 2.—FLEX COMPARISON

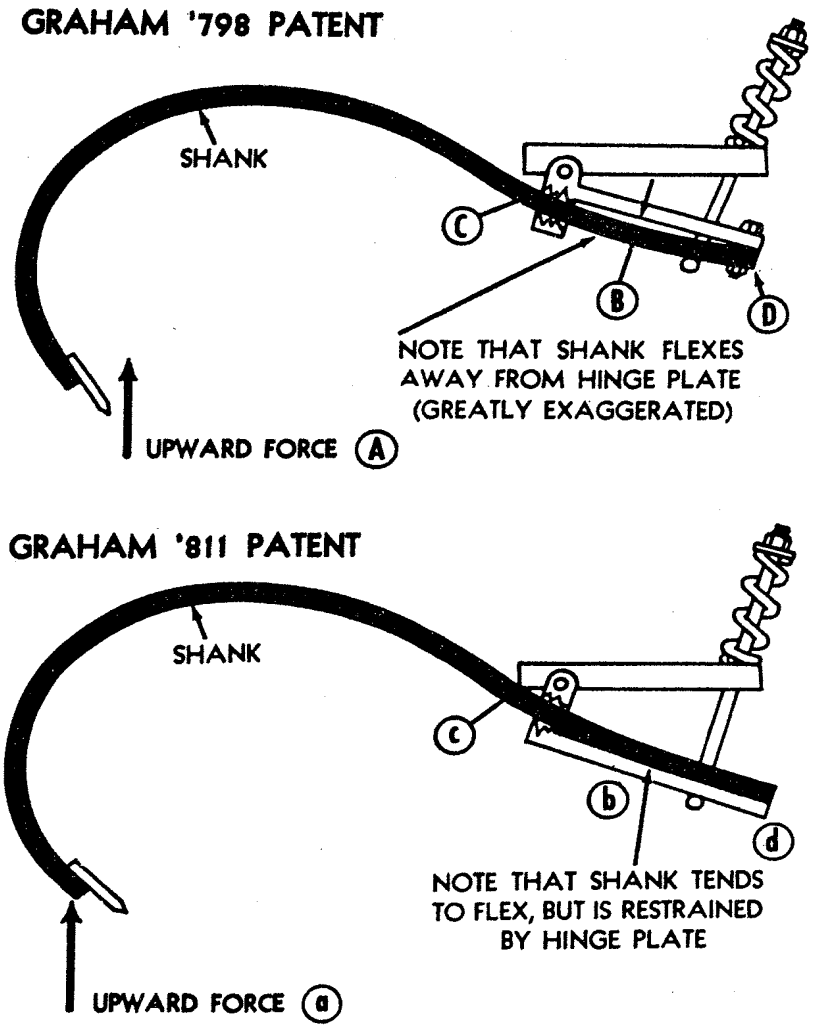

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FIG. 3. SCOGGIN PATENT 2,870,943
(The Patent in Issue)

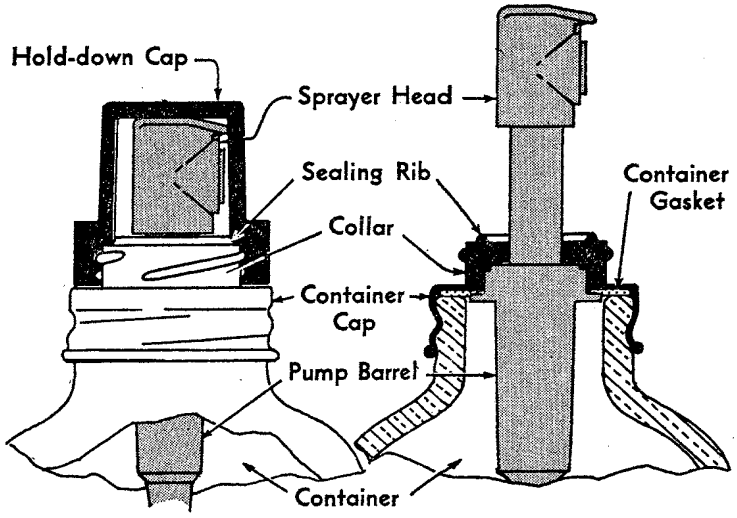


FIG. 4. LOHSE PATENT 2,119,884
(Prior art 1938)

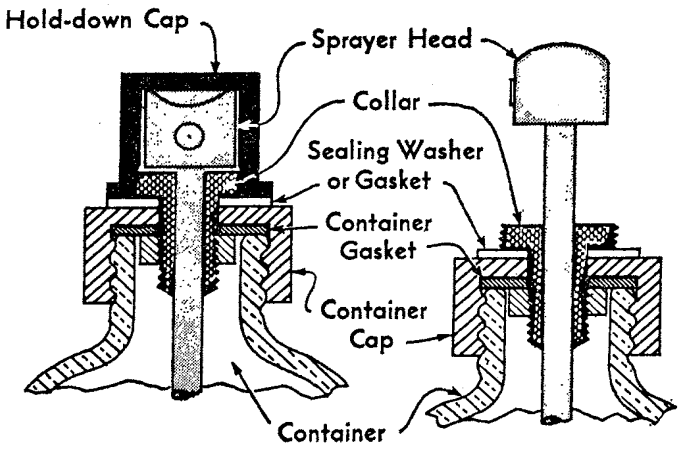


FIG. 5. MELLON PATENT 2,586,687
(Prior art 1952)

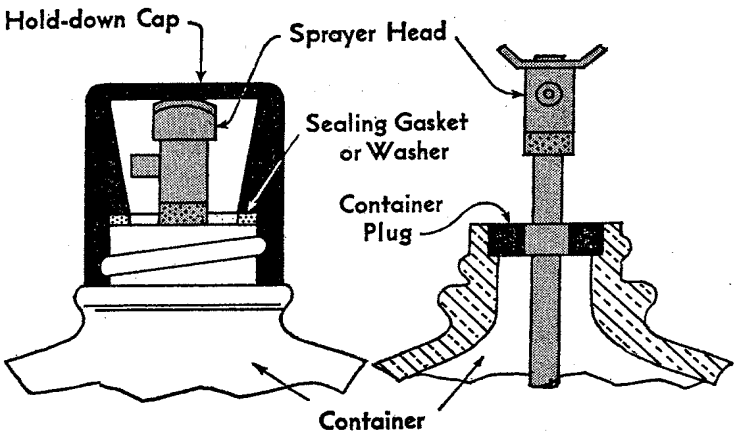
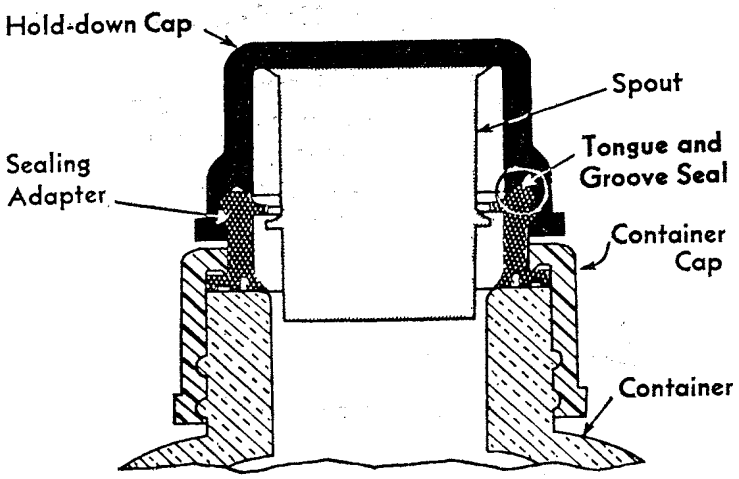


FIG. 6. LIVINGSTONE PATENT 2,715,480
(Prior art 1953)



Court of Appeals, Federal Circuit

In re Grasselli and Hardman,
and Rohm and Haas Company, Intervenor

No. 83-504
Decided July 15, 1983

PATENTS

1. Pleading and practice in Patent Office — Rejections (§54.7)

Rejections under 35 USC 103 must be based on evidence comprehended by that section's language.

2. Patentability — Invention — In general (§51.501)

Inherency issue is question of fact.

3. Patentability — Invention — Specific cases — Chemical (§51.5093)

Known relationship of lithium, cesium, rubidium, and francium to sodium and potassium, as Group IA elements, is not sufficient, in and of itself, to treat them as interchangeable in catalyst compositions.

4. Board of Appeals — Procedure after hearing or appeal (§19.40)
Court of Appeals for the Federal Circuit — Jurisdiction (§26.55)

Patent Rule 198 proscriptions, relating to proceedings after Board of Appeals' decision, are not relevant to case remanded to examiner by board under Rule 196(d); under Rule 196(d), board decision including remand is not considered as final decision in case; accordingly, under express provisions of rule, board, after remand proceedings, either adopts its decision as final or renders new decision on all of claims on appeal; express PTO policy interpreting Rule 196(d) suggests that decision containing remand is not appealable under 35 USC 141.

5. Patentability — Evidence of — In general (§51.451)

Objective evidence of nonobviousness must be commensurate in scope with claims that evidence is offered to support.

6. Patentability — Evidence of — In general (§51.451)

Comparison of claimed catalyst with most similar catalyst, which is appellant's, that shows that claimed catalyst outperformed others and conclusion that this is evidence of unexpected superiority is ultimate extension of "indirect showing of unexpected superiority" sanctioned by precedent.

7. Patentability — Anticipation — Combining references (§51.205)

Express descriptions of two references over which claims in issue were rejected that indicates that components of two catalysts are not interchangeable is material to validity of rejection of catalyst composition claims under 35 USC 103.

Particular patents — Catalyst

Grasselli and Hardman, Process for the Manufacture of Isoamylenes and Methyl Butanols and Catalyst therefor, rejection of claims 1-14, 16-18, 33, and 34 affirmed and rejection of claims 15 and 19-32 reversed.

Appeal from Patent and Trademark Office Board of Appeals.

Application for reissue of patent of Robert K. Grasselli and Harley F. Hardman, Serial No. 713,024, filed Aug. 9, 1976, to reissue Patent No. 3,642,930, issued Feb. 15, 1972, on application, Serial No. 867,934, filed Oct. 20, 1969, continuation in part of application, Serial No. 794,469, filed Dec. 30, 1968. From decision rejecting claims 1-34, applicants appeal (Rohm and Haas Company, intervenors). Affirmed in part and reversed in part.

Ford F. Farabow, Jr., Washington, D.C. (David W. Hill and George W.F. Simmons, both of Washington, D.C., of counsel) for appellants.

Dale H. Hoscheit, Washington, D.C., for intervenor

Before Bennett, Smith, and Nies, Circuit Judges.

Nies, Circuit Judge.

This appeal is from the decision of the United States Patent and Trademark Office (PTO) Board of Appeals (board) affirming the final rejections under 35 U.S.C. §103 (1976) of claims 1-34, all of the claims of reissue application serial No. 713,024 filed August 9, 1976. We reverse with respect to claims 15 and 19-32 and affirm the board's decision with respect to all other claims.

I.

The original patent sought to be reissued here, U.S. Patent No. 3,642,930 (issued on

February 15, 1972, to Standard Oil Company, Cleveland, Ohio), is directed to catalysts containing an alkali metal as an essential catalytic ingredient. As claimed, the catalyst composition must contain, in addition to the alkali metal, bismuth, iron and molybdenum in oxide form.[1] Such alkali metal catalyst compositions are asserted, in the patent, to be an improvement over prior art catalysts in that they are particularly suited to the catalytic oxydehydrogenation of isoamylenes, methyl butanols, or mixtures thereof to isoprene.

By this reissue application under 35 U.S.C. §251 (1976), inventors Grasselli and Hardman (hereafter appellants) have presented claims additional to those of the patent: claims directed to catalysts requiring the essential alkali metal component to be potassium, cesium, or rubidium; claims requiring inclusion of preferred additives, and claims requiring activation of the catalyst at 500°F and up to 1250°F.

Specifically, the subject application for reissue sets forth claims to a catalyst composition in claims 6-34, and to a process for catalytic isoprene production in claims 1-5. Claims illustrative of that process and catalyst composition are set forth below:

1. The process for the conversion of isoamylenes, methyl butanols or mixture thereof to isoprene comprising contacting said isoamylenes, methyl butanols or mixtures thereof with a molecular oxygen-containing gas over a catalyst consisting essentially of an activated catalytic oxide complex described by the following formula:

$Bi_aFe_bMo_cQ_dR_eT_fM_gO_x$

wherein Q is an alkali metal,
R is an alkaline earth metal,
T is phosphorus, arsenic or antimony,
M is cobalt and/or nickel, and
wherein a, b and c are numbers in the range of
0.1 to 12, d is a number from 0.1 to 8,
e is a number from 0 to 8,
f is a number from 0 to 6,
g is a number from 0 to 12, and
x is a number determined by the valence requirements of the other elements present,

in a reaction zone maintained at from above 500°F to about 1100°F. at from about 0.5 to about 10 atmospheres pressure with a contact time of from about 0.01 second to 50 seconds, and recovering the isoprene.

6. A catalyst composition consisting essentially of an activated catalytic oxide complex of an alkali metal, bismuth, iron and molybdenum as essential catalytic ingredients, and defined by the following formula:

$Bi_aFe_bMo_cQ_dR_eT_fM_gO_x$

wherein Q is an alkali metal,
R is an alkaline earth metal,
T is phosphorus, arsenic or antimony,
M is cobalt and/or nickel, and
wherein a, b and c are numbers in the range of 0.1 to 12,
d is a number from 0.1 to 8,
e is a number from 0 to 8,
f is a number from 0 to 6,
g is a number from 0 to 12, and
x is a number determined by the valence requirements of the other elements present.

7. The composition of claim 6 wherein Q is potassium.

14. The composition of claim 7 wherein M is cobalt and wherein activation of the catalytic oxide complex is conducted at 500°F to 1250°F in the presence of an atmosphere consisting essentially of air.

15. The composition of claim 6 wherein Q is potassium and M is cobalt, and wherein e equals O, f equals O and g is a number larger than O.

17. The composition of claim 7 wherein activation of the catalytic oxide complex is conducted at 500°F in the presence of an atmosphere consisting essentially of air.

19. The composition of claim 6 wherein Q is cesium.

26. The composition of claim 6 wherein Q is rubidium.

As can be seen from the above, the preferred alkali metals, potassium, cesium, and rubidium, are recited in claims 7, 19 and 26. Claims 14 and 17 recite the temperature at which the catalyst compositions can be activated. Catalyst composition claims, depending from claims 6, 7, 19 and 26, refer to inclusions of optional components expressly recited in claim 6, specifically phosphorus (claims 8, 23 and 30); cobalt (claims 9, 14, 15, 21, 28, 34); nickel (claims 10, 13, 20, 27, 33); mixtures of cobalt and nickel (claim 12); antimony (claims 16, 24, 29) and arsenic (claims 22, 31). Other claims depending from claims 7, 19 and 26 specify that the catalyst is supported on silica (claims 18, 25 and 32).

II.

Notwithstanding its expedited case status,

[1] In the discussion below, this base catalyst is referred to as a four-component catalyst.

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ıds, and recovering the

nposition consisting es-
tivated catalytic oxide
li metal, bismuth, iron
s essential catalytic in-
ned by the following

M_gO_x
ali metal,
arth metal,
arsenic or antimony,
or nickel, and
e are numbers in the

n 0.1 to 8,
n 0 to 8,
n 0 to 6,
n 0 to 12, and
rmined by the valence
the other elements

ı of claim 6 wherein Q

on of claim 7 wherein
rein activation of the
olex is conducted at
ı the presence of an
; essentially of air.
on of claim 6 wherein
l M is cobalt, and
f equals O and g is a
).

n of claim 7 wherein
ytic oxide complex is
n the presence of an
essentially of air.
n of claim 6 wherein

ı of claim 6 wherein

the above, the pre-
assium, cesium, and
claims 7, 19 and 26.
the temperature at
ositions can be acti-
on claims, depending
l 26, refer to inclu-
nts expressly recited
iosphorus (claims 8,
is 9, 14, 15, 21, 28,
3, 20, 27, 33); mix-
(claim 12); antimo-
l arsenic (claims 22,
ling from claims 7,
catalyst is support-
and 32).

pedited case status,

the instant reissue application has been pending for seven years. The many issues, considered in this appeal, are in part attributable to the efforts of Rohm and Haas who vigorously protested this reissue, by appearance during ex parte prosecution, by briefing and oral arguments before the board, and here as an intervenor.[2]

These reissue proceedings have twice been appealed to the board. Consequently, two decisions by the board are being reviewed here. As a result of both decisions, there are twelve separate grounds of rejection of the claims, all under 35 U.S.C. §103,[3] which were affirmed by the board and are the subject of this appeal.

During the first appeal, the board affirmed the examiner's final rejections, based on the following four references which disclose alkali metals, or compounds thereof, in catalysis processes.

Japanese Patent Publication No. 41-11847/1966, June 29, 1966 (Japanese Patent)
U.S. Patent No. 3,205,280 — Wattimena et al. (U.S. Wattimena)
U.S. Patent No. 3,621,072 — Watanabe et al. (Watanabe)
U.S. Patent No. 3,415,886 — McClellan (McClellan)

The Japanese Patent Publication No. 41-11847/1966 (Japanese Patent) was cited as a "new ground" of rejection in the examiner's answer in the first appeal to the board as a result of five affidavits, filed by Rohm and Haas, apparently purporting to show that Example 4 of the Japanese Patent produced a product within appellants' claims.

The examiner did not make the additional rejections based on other prior art references as suggested by Rohm and Haas.

However, in the board's first decision, pursuant to its authority under 37 C.F.R. §§1.196(b) and 1.196(d) (Rules 196(b) and 196(d)),[4] the board did entertain Rohm and Haas's suggestions to make those additional rejections on the following references:

[2] The Rohm and Haas motion to intervene here was granted in view of Rohm and Haas's status as a protestor in these reissue proceedings and because the catalyst that Rohm and Haas uses for the oxidation of propylene to acrolein (a catalytic oxidation of an olefin to an unsaturated aldehyde) was accused in an International Trade Commission ("ITC") proceeding of infringing the Grasselli and Hardman catalyst claims. See Rohm & Haas v. ITC, 554 F.2d 462, 193 USPQ 693 (CCPA 1977). The ITC proceedings were terminated at Standard Oil's behest prior to a determination on the merits, following which Standard Oil sought reissue.

[3] §103 provides:
§103. Conditions for patentability; non-obvious subject matter
— A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[4] §1.196(b) provides:
(b) Should the Board of Appeals have knowledge of any grounds not involved in the appeal for rejecting any appealed claim, it may include in the decision a statement to that effect with its reasons for so holding, which statement shall constitute a rejection of the claims. The appellant may submit an appropriate amendment of the claims so rejected or a showing of facts, or both, and have the matter reconsidered by the primary examiner. The statement shall be binding upon the primary examiner unless an amendment or showing of facts not previously of record be made which, in the opinion of the primary examiner, avoids the additional ground for rejection stated in the decision. The appellant may waive such reconsideration before the primary examiner and have the case reconsidered by the Board of Appeals upon the same record before them. Where request for such reconsideration is made the Board of Appeals shall, if necessary, render a new decision which shall include all grounds upon which a patent is refused. The appellant may waive reconsideration by the Board of Appeals and treat the decision, including the added grounds for rejection given by the Board of Appeals, as a final decision in the case.
§1.196(d) provides:
(d) Although the Board of Appeals normally will confine its decision to a review of rejections made by the primary examiner, should it have knowledge of any grounds for rejecting any allowed claim that it believes should be considered, it may include in its decision a statement to that effect and remand the case to the primary examiner for consideration thereof. In such event, the Board shall set a period, not less than one month, within which the appellant may submit to the primary examiner an appropriate amendment, or a showing of acts or reasons, or both, in order to avoid the grounds set forth in the statement of the Board of Appeals. If the primary examiner rejects the previously allowed claim or claims on the basis of such statement, the appellant may appeal to the Board of Appeals from the rejection. Whenever a decision of the Board of Appeals includes a remand, that decision shall not be considered as a final decision in the case, but the Board of Appeals shall, upon conclusion of the proceedings before the primary examiner on remand, either adopt its decision as final or render a new decision on all of the claims on appeal, as it may deem appropriate.

U.S. Patent No. 3,226,442 — Sennewald et al.
U.S. Patent No. 3,346,617 — Hiroki et al.
U.S. Patent No. 3,414.631 — Grasselli et al. (Grasselli '631)
U.S. Patent No. 3,454,630 — Yamaguchi et al.
British Patent 973,565 — Wattimena et al. (British Patent)

Specifically, the board's first decision contained a recommendation to the examiner, in accordance with Rule 196(d), to reconsider the examiner's allowance of certain claims in view of the above references. After remand of the case to the examiner, and during prosecution before him, various declarations and affidavits were presented by both Rohm and Haas and appellants. Relying on 37 C.F.R. §1.198,[5] the examiner refused to consider appellants' declarations and affidavits, after having specifically been entered by petition to the Commissioner, on the ground that the experiments therein related only to rejections affirmed by the board in its first decision.

Since the board's second decision is expressly limited to consideration of the rejections originally proposed by the board under Rules 196(b) and 196(d), the board apparently adopted, at least in part, the examiner's reasoning for refusing to consider appellants' affidavits and declarations filed during the remand period.

As a result of the subsequent prosecution and the board's second decision, all of appellants' claims (original as well as new claims) stand rejected under 35 U.S.C. §103. Specifically, the following grounds apply:

Claims	References
1-7,11, 19, 25, 26, 32	U.S. Wattimena
11, 16, 19, 23-26, 29, 30, 32	Watanabe
1-15, 18-21, 23, 25-28 30, 32-34	McClellan
6, 7, 11-15, 18-21, 25-28, 32-34	Japanese Patent
12-15, 18, 20, 21, 27, 28, 33, 34	U.S. Wattimena taken with the British Patent
16, 24, 29	McClellan taken with Grasselli '631
16, 24, 29	Japanese Patent
6-8, 11, 16, 19, 23-26, 29, 30, 32	Sennewald et al. in combination with Hiroki et al.
5, 9-13, 15-16, 18-34	Yamaguchi et al., or Grasselli '631 taken with Watanabe
17, 22, 31	Sennewald et al. in combination with Hiroki et al.
22, 31	Grasselli '631 in view of Watanabe and appellants' admissions
17, 22, 31	McClellan in view of Grasselli '631

[5] §1.198 provides:
Cases which have been decided by the Board of Appeals will not be reopened or reconsidered by the primary examiner except under the provisions of §1.196 without the written authority of the Commissioner, and then only for the consideration of matters not already adjudicated, sufficient cause being shown.

III.

To set the context of the issues here, it is emphasized that all rejections made by the PTO are under 35 U.S.C. §103. No written description of a catalyst embraced by the appealed claims appears in the prior art applied in the various rejections. In re Marshall, 578 F.2d 301, 198 USPQ 344 (CCPA 1978); In re Arkley, 455 F.2d 586, 172 USPQ 524 (CCPA 1972). However, Rohm and Haas put forth a theory of inherency, normally the basis for rejection under 35 U.S.C. §102, that the board apparently adopted.

In any event, the issues here relate to the determination of obviousness, or nonobviousness, of claims directed to a catalyst composition with four essential components: bismuth, iron, molybdenum and an alkali metal, as well as to claims of a method using that catalyst.

Appellants take the position that none of the rejected claims would have been prima facie obvious from the prior art. In essence, appellants argue that catalysis is unpredictable and that the board has equated very different catalysts and very different reactions with those of appellants to support the rejections.

Alternatively, if the claims appear to have been prima facie obvious, appellants argue that rebuttal evidence of record negates this conclusion. Primarily, appellants rely on Friedrich I, Friedrich II, Friedrich III and Friedrich IV declarations, although other declarations (and affidavits) were filed on behalf of appellants corroborating, supporting, or adding to information set forth in the four Friedrich declarations.[6] Specifically, appellants ask this court to consider, although the board did not, the experiments and evi-

[6] These are by Baldwin, Strecker, Callahan and Grasselli et al. Rohm and Haas, too, has filed various declarations and affidavits. These are by Kennelly, De Jong, Lade, Bauer and Nemec.

References

Yamaguchi et al., or Grasselli '631 taken with Watanabe

Sennewald et al. in combination with Hiroki et al.

Grasselli '631 in view of Watanabe and appellants' admissions

McClellan in view of Grasselli '631

II.

of the issues here, it is rejections made by the .S.C. §103. No written ılyst embraced by the ırs in the prior art ap- ections. In re Marshall, PQ 344 (CCPA 1978); d 586, 172 USPQ 524 :ver, Rohm and Haas nherency, normally the :r 35 U.S.C. §102, that ıdopted.

sues here relate to the ıśness, or nonobvious- ! to a catalyst composi- ! components: bismuth, d an alkali metal, as a method using that

position that none of ɔuld have been prima prior art. In essence, catalysis is unpredict- ırd has equated very ʼery different reactions ants to support the

claims appear to have ɔus, appellants argue of record negates this appellants rely on II, Friedrich III and ions, although other .avits) were filed on rroborating, support- ıation set forth in the ·ations.[6] Specifically, to consider, although experiments and evi-

Strecker, Callahan and d Haas, too, has filed ffidavits. These are by Bauer and Nemec.

dence of Friedrich III and IV with respect to rejections affirmed by the board in its first decision.

IV.

The examiner held that appellants' claimed catalyst and method of use would have been obvious on the basis of teachings in any one of the following references: Japanese Patent; U.S. Wattimena, Watanabe, or McClellan. These four references were asserted as four separate grounds of rejection which were the subject of the first appeal. As the PTO treated these four references as the references most material to the issue of patentability of all of the rejected claims, they will be considered first; for analysis, we find it convenient to discuss them starting with Watanabe.

A.

Watanabe (U.S. Patent No. 3,621,072)

Appellants argue, and we agree, that the board erred in holding that any of appellants' claims would have been obvious from the teachings of Watanabe.[7]

Watanabe describes a catalytic conversion of a mixed gas of isobutylene, methanol and/or ethyl ether to isoprene. The catalyst used by Watanabe is described to be at least one oxide of tungsten, vanadium, molybdenum, uranium, copper, iron, and chromium. Various Watanabe examples employ as the catalyst one oxide of the aforementioned elements; one of the examples employs as a catalyst a mixed oxide system of molybdenum-vanadium-uranium-tungsten.

In the board's view Watanabe is pertinent under 35 U.S.C. §103 for the sole reason that:

> We note the explicit *suggestion* by these patentees *to add* compounds of *alkali metals such as sodium or potassium* to the catalysts, to increase isoprene selectivity. [Emphasis added.]

Watanabe describes the addition of promoters to the catalyst, to inhibit side reactions and increase product selectivity. These promoters are described to be compounds of phosphorus, sulfur, boron, antimony, bismuth, tellurium, silver, barium, calcium, magnesium, potassium and sodium. Of the 22 Watanabe examples, 10 describe the use of promoters. None of the specific examples relies on the use of sodium or potassium as a promoter.

The "promoted catalysts" actually described therein — oxides of the following systems: uranium-antimony; tungsten-tellurium; molybdenum-phosphorus; molybdenum-sulfur; vanadium-sulfur; molybdenum-bismuth-phosphorus and calcium-bismuth-molybdenum-phosphorus — differ significantly from the subject compositions. Even if sodium or potassium were substituted, in any one of the exemplified "promoted" catalysts, for the identified promoter(s), and were operative therein, any composition thus created is deficient in at least one element of appellants' catalyst and there is no objective basis to add the missing element(s) to create the composition as claimed. Thus, appellants' catalyst composition cannot be held to have been obvious from Watanabe alone.

B

Wattimena (U.S. Patent No. 3,205,280)

U.S. Wattimena describes butene production by dehydrogenating butane in the presence of a halogen, oxygen and a solid catalyst.[8]

According to U.S. Wattimena, the solid catalyst must contain "one or more alkali metal and/or alkaline-earth metal compounds"; and the preferred catalysts are reported to be those composed of potassium bromide, silver bromide and didymium chloride, on a support. U.S. Wattimena broadly suggests enhanced activity of the basic catalyst on "addition" of "one or more metal compounds derived from the transition elements of Groups I and IV to VIII of the Periodic Table and/or a rare-earth metal compound,"

[7] Although appellants had argued in the first appeal, and do here, that Watanabe "falls short of establishing a prima facie case or obviousness," appellants filed a declaration under 37 C.F.R. §1.131 "in order to simplify the issues on appeal," during the remand period between the first and second appeals to the board. In the board's second decision, the board reversed the rejections of certain claims over Watanabe, finding the declaration sufficient to antedate the reference with respect to those claims. As the Watanabe reference does not establish a prima facie case of obviousness, we need not treat the remaining issues arising under 37 C.F.R. §1.131.

[8] Although it appears from the discussion above, in section II, that U.S. Wattimena and the British Patent (British Patent No. 973,565 to Wattimena) are used in two different grounds of rejection, this is not the case. The examiner and the board treated the British Patent to be cumulative to U.S. Wattimena. For purposes here, we will agree with the examiner and the board, in a way as adverse to appellants as possible, that the British Patent confirms the intention of U.S. Wattimena to disclose bismuth as a potential catalytic component.

such as the elements: zirconium, titanium, vanadium, chromium, molybdenum, manganese, tungsten, iron, cobalt, nickel, palladium, copper, silver and compounds thereof.

The rejections under 35 U.S.C. §103 over Wattimena are based on the following description:

> A suitable *solid catalyst (plus carrier)* for the dehydrogenation of butene to butadiene has the following composition (in parts by weight): $A1_2O_3$ 90.2; SiO_2 9.0; Fe_2O_3 0.2; MgO 0.1, CaO 0.1; Na_2O 0.1; K_2O 0.1; and TiO_2 0.1. A catalyst which was successfully used in the dehydrogenation of n-butane contained, in addition, 1.7 "didymium oxide." 0.6 Na_2O, and 1.4 MoO_3, the latter compounds as Na-molybdate. In another similar case, the additional compounds consisted of 11.4 Bi_2O_3 and 7.0 MoO_3 parts by weight. Excellent results were also obtained with a solid catalyst consisting of 100 SiO_2; 19.9 "didymium oxide"; 17.1 MoO_2 and 3.7 Na_2O parts by weight.

U.S. Wattimena, col. 4, lines 38-49 (emphasis added).

As framed by the parties, the issue posed by Wattimena resides in an *interpretation* of the description of the first composition of eight components ($A1_2O_3$, SiO_2, Fe_2O_3, MgO, CaO, Na_2O, K_2O and TiO_2), particularly in light of the language "solid catalyst (plus carrier)." Two extremely divergent views in interpreting this description have been argued.

On the one hand, it is argued that appellants' catalyst, for example as in claim 6, would have been obvious from the whole of the above excerpt from Wattimena inasmuch as the four components of appellants' catalyst would be found together if Bi_2O_3 and MoO_3 are added as suggested in the third sentence of the above excerpt, (albeit as a ten-component composition);[9] however, it is noted, the excerpt fails as a direct anticipation because, inter alia, the eight-component composition contains TiO_2, described as a catalytic component by U.S. Wattimena but not recited in appellants' claims as a catalytic component.

On the other hand, appellants argue that the eight-component composition described in the excerpt above must be construed as constituting a *carrier*. To buttress this argument, appellants rely on information in brochures, as well as other evidence in the record of this appeal, which shows that Norton alpha aluminas (catalyst carriers) comprise each of the eight components ($A1_2O_3$, SiO_2, Fe_2O_3, MgO, CaO, Na_2O, K_2O and TiO_2) in substantially similar, though not identical, proportions to the eight-component composition in the Wattimena description excerpted above and relied upon by the PTO in the rejections under 35 U.S.C. §103[10]

In our view, the effect of this information concerning the composition of the Norton alpha-alumina carrier is not to interpret what was intended by Wattimena's description, but to shift the burden of going forward to the PTO. It then became incumbent on the PTO to show that Wattimena itself would suggest adding two components and selecting out at least the four essential components of appellants' catalyst, or that there was some reasonable basis in the prior art to make the selection claimed here. See In re Sasse, 629 F.2d 675, 681, 207 USPQ 107, 111-12 (CCPA 1980). The PTO failed to counter appellants' showing and, accordingly, we do not sustain claim rejections based on U.S. Wattimena.

C.

The Japanese Patent Publication 41-11847 (Japanese Patent)

The Japanese Patent is directed to improving the selectivity of a known process for producing propylene oxide (the epoxide) by decreasing isomerization reactions which result in the by-product propionaldehyde. This improvement is achieved by modification of

[9] Declarations filed by Friedrich (Friedrich I) and Strecker on appellants' behalf have been considered. These declarations attempt to show that the written description fails to produce appellants' catalyst and pertains to X-ray study comparisons of the eight-component composition, described in Wattimena, excerpted above, and of the composition resulting from the addition of Bi_2O_3 and MoO_3 to that eight-component composition. These declarations are not considered to be dispositive of the issue attempted to be proven, as there is, inter alia, no X-ray study of a four-component catalyst, of, for example, appealed claim 6, in the study.

[10] The evidence, brochures and other information, includes an April 4, 1977, letter from James D. Ball of Norton Company Chemical Process Products Division; a typical chemical analysis of the SA-5105 (SA-105) catalyst carrier, a Norton alpha-alumina; Bulletin CC-10 entitled "Catalyst Carrier," (1974); a chemical analysis sheet for SA-5205, augmenting information in Bulletin CC-10; and a comparison of the old product, the then current (1977) product and the product sent to Standard Oil Company.

The Baldwin declaration confirms the fact that Norton alpha aluminas (for example, Norton SA 105) predate the application filing date of the original patent sought to be reissued; none of the arguments here dispute that fact.

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process conditions but does not rely on use of any particular catalyst system.

In fact, the Japanese Patent suggests no criticality as to the catalyst composition. That is, the Japanese Patent indicates that any "metal and/or metallic oxide system" based on "copper, silver, molybdenum, bismuth, vanadium, antimony, tungsten, cobalt, nickel, manganese, chromium, tin, selenium, or iron" may constitute the catalyst. Catalysts used in Examples 1-3 and 5-12 vary widely in composition, for example, from silver or silver oxide alone to systems including copper, tin, and selenium.

The contribution of the Japanese Patent, the modification of the propylene oxide production process conditions to improve selectivity, requires both *inclusion of a peroxide* or a peroxide source in the feed stream of propylene and oxygen *and* addition of a *basic organic or inorganic substance* (hereinafter "basic modifier") to an "ordinary" oxidation catalyst of a metal and/or metallic oxide system. The basic modifier is broadly described as organic or inorganic, solid or liquid, either a strong base or a weak base. In the examples, triethanol amine, 2,3,4-trimethyl pyridine, sodium carbonate, sodium hydroxide and potassium hydroxide are used as the source of the basic modifier.[11]

Within the confines of the patent, a number of examples of the improved process are given. But for Example 4, the entire disclosure is otherwise of no interest.

In Example 4, the first stage in the process requires admixing potassium hydroxide (as the source of the modifier) with stearic acid containing a calcined mixture of the salts of bismuth, iron and molybdenum. The pertinent portion of Example 4 reads:

Example 4:

> 110 gm of ammonium molybdate was dissolved in 150 cc of hot water. Separately a dispersion of 150 gm of bismuth nitrate and 50 gm of ferric nitrate in 100 cc of 1N nitric acid solution was prepared. The solutions were mixed to form a milky brown precipitate. The precipitate was dried at 110°C, crushed, 1% by weight of stearic acid added and molded to circular tablets 5 mm diameter x 5 mm, then calcined at 400°C for 16 hours. The catalyst thus obtained is referred [to] as Catalyst-C (comparative example).
>
> 15 cc of 1N potassium hydroxide solution was added to the Catalyst C and the product obtained by drying it at 120°C is referred [to] as Catalyst D (example of this invention).

It is apparent that no written description of the claimed compositions is given in Japanese Patent Example 4 and the board refused to hold the Japanese Patent to be a direct anticipation. In re Arkley, 455 F.2d 586, 172 USPQ 524 (CCPA 1972). Without explanatory comment, the board, nevertheless, adopted the examiner's reasons for affirmance of the §103 rejections based *not* on any interpretation of the *prior art* embodied by the Japanese Patent, but on extraneous evidence in the form of affidavits filed by Rohm and Haas during the examination of the subject reissue application in support of its assertion that appellants' catalyst was anticipated by Japanese Patent Example 4, a position it urged before the board.

[1] It is fundamental that rejections under 35 U.S.C. §103 must be based on evidence comprehended by the language of that section. In re McKellin, 529 F.2d 1324, 1329, 188 USPQ 428, 433 (CCPA 1976). We consider the affidavits not because of their competency as prior art but rather because of the *inferences* of *inherency* which underlie the PTO's §103 rejections based on the Japanese Patent and which are not consistent with the description of the Japanese Patent, set forth above. If the affidavits fail to show that Japanese Patent Example 4 produces a composition within the rejected claims, a fortiori, they evidence nothing relevant to the patentability of the rejected claims.

Inherency would be established either if the portion of Example 4 excerpted above produces the four-component catalyst; or if the Example 4 catalyst is converted to the four-component catalyst when it is subjected to temperatures of propylene oxide production described in other portions of Example 4.

[2] The issue of inherency is a question of fact. In re Fracalossi, 681 F.2d 792, 794, 215 USPQ 569, 571 (CCPA 1982). Five affidavits, apparently presented by Rohm and Haas to support the above two arguments, fail to establish such critical facts. The affidavits state that a reaction product is formed (by a test with pH paper) when the potassium hydroxide is added to the stearic acid containing the calcined mixture of salts of bismuth, iron, and molybdenum when the synthesis of Japanese Patent Example 4 is followed, and that the potassium content of that reaction product remains substantially constant, whether it is merely dried at 120°F or subsequently heated at 340°C, or heated to 427°C, and then to 538°C. However, there is no evidence that that reaction product is one embraced by claims 6 and 7. Specifically,

[11] Significantly, the Japanese Patent does not describe "alkali metal(s)" either in conjunction with the description of the catalyst or in conjunction with the basic modifier.

there is no evidence of record which shows that that reaction product includes potassium in the potassium oxide form.[12] If appellant's catalyst is inherent in the Japanese Patent, it has not been established by the record here and obviousness cannot be predicated on that which is unknown. Thus, we reverse the board's rejection on the Japanese Patent.

D.

McClellan, U.S. Patent No. 3,415,886

McClellan, U.S. Patent No. 3,415,886, is directed to bismuth molybdate-, or phosphobismuth molybdate- (bismuth molybdate), on silica catalysts heat treated to temperatures of 750° to 850°C to convert crystalline bismuth molybdate to an amorphous phase. Heat treatment to achieve this result may be undertaken in two stages, first at a temperature of 400 to 500°C and then at a temperature of 750 to 850°C. These catalysts are described to be useful in oxydative dehydrogenation, in propylene ammoxidation and isoprene production.

The significance of McClellan resides in its additional descriptions, relating to the presence of alkali metal in the catalyst and to the enhancement of catalytic activity by inclusion of promoters such as iron. Appellants argue, however, that McClellan actually teaches away from inclusion of alkali metal in the catalyst and, that as to promoters, McClellan contains merely a "shot-gun" description of many elements for such use, which would not lead a person of ordinary skill to select the elements appellants require.

With respect to alkali metal inclusion, McClellan suggests that sodium and/or potassium may *contaminate* the McClellan heat treated catalyst if reactants containing sodium or potassium are employed, as a source of the molybdate, or if the silica sol used as the essential silica carrier contains either or both:

> Molybdenum oxide is usually obtained from aqueous ammonium molybdate; however, alkali molybdates can be used. When alkali molybdates such as sodium or potassium molybdate are used, sodium or potassium ion, which is difficult to eliminate completely, must be acceptable in the final catalyst. An atomic Na:Mo ratio of 1:4 must not be exceeded in order to maintain good directivity in the catalyst. After processing in the manner described in this invention, heat-treated compositions containing sodium or other alkali or alkaline earth metals in the acceptable metal/molybdenum ratio of 1:4 or less give X-ray evidence of the presence of the scheelite structure of crystalline $Mx_1/xBiMo_2O_3$, where x = valence of alkaline earth or alkali metal M. In view of the desirability of low sodium and potassium content in most catalysts, ammonium molybdate is a preferred source of the molybdenum component of the catalyst.
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>
> The catalyst of the invention involves use of silica as a support, and the silica must be added as colloidal silica, i.e., an aqueous silica sol (silica sols generally contain about 30-40% silica). The silica can be present in the final catalyst in any amount less than 90% and greater than 5%, but it is preferred that the catalyst contain about 27-75% by weight of silica. Certain commercial silica sols contain small amounts of sodium (e.g., one commercially available product of 30% SiO_2 content contains 0.3% Na_2O as titratable alkali), but, as previously discussed, low levels of sodium appear to have no serious effect on the catalysts of this invention. When these commercial silica sols are used, the catalytic composition can have the following formula:
>
> $Bi_a P_b Mo_{12} Si_c O_d Na_e$ where a is 4, b is 0 to 2, c is 24 to 160, d is 1.5a + 2.5b + 36 + 2c + 0.5e and e is 0 to 3.

McClellan, col. 3, lines 1-65.

Although McClellan does indicate that sodium and/or potassium can adversely affect the "directivity" of catalysts, as well as methods for insuring the absence of alkali metal, McClellan's catalyst will tolerate sodium and/or potassium contamination to a specified extent. Moreover, Example 1 of the reference describes, as a result of McClellan's heat treatment (at 750°C), an amorphous scheelite $NaBiMo_2O_8$ catalyst.[13] McClellan

[12] Moreover, the evidence in Friedrich II and Friedrich III comparing the catalyst of the Japanese Patent Example 4 to appellants' four-component catalyst, containing potassium as the essential alkali metal, shows that under certain catalytic reaction conditions the activity of appellants' four-component catalyst differs substantially from that produced by the Japanese Patent Example 4 and that activity is independent of amounts of potassium hydroxide used.

[13] Appellants argue that the language "activated catalytic oxide complex" in claims 1 and 6 and the language in claims 17 and 14 specifying temperatures of 500°F and 500 to 1250°F, respectively, as temperature of catalyst activation, serve as patentable distinction over McClellan which requires an ultimate calcination temperature of 750°-850°C. However, McClellan does indicate that the first

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catalyst and the efficacy of the resulting composition for its intended use as a catalyst. The only missing ingredient is iron which, however, McClellan supplies.

To enhance catalytic activity, McClellan enumerates iron, nickel, or cobalt, as well as various other elements, as promoters. Appellants argue that many elements are enumerated as promoters and that no specific promoted *catalyst* is described in McClellan. However, McClellan specifically indicates that addition of the promoters, iron, for example, (as well as "cobalt and nickel," recited in other claims) will enhance catalytic activity. Moreover, McClellan specifically describes how to apply these promoters:

> These promoters are usually applied by impregnation or surface coating of already formed bismuth molybdate of phosphomolybdate-on-silica catalysts. Thus, the metals can be added to the slurried catalyst as a salt or acid or the metal, e.g., as a compound which is thermally decomposable in situ to form the desired promoter. After the catalyst has been impregnated with such solutions, employed in concentrations adequate to provide the desired amount of material, the impregnated catalyst may be dried and calcined *at any desired temperature.*

McClellan, col. 5, lines 2-11 (emphasis added).

The descriptions of McClellan directed to adding iron, nickel and cobalt as promoters, how to make that addition, and the effect of that addition, once made, suggest a predictably operative result, a successful addition to those elements to McClellan's catalyst. In re Mercier, 515 F.2d 1161, 185 USPQ 774 (CCPA 1975).

In view of the McClellan description concerning the addition of *iron* as a promoter and the express statement concerning the tolerance of McClellan catalysts to limited amounts of sodium and potassium ion, we agree with the board that appellants' claimed catalyst composition of these four elements and claimed method would have been prima facie obvious from McClellan and in the absence of evidence to overcome this prima facie case the rejections of claims 1-15, 18, 33 and 34 must be affirmed.

However, we do not agree that McClellan also renders obvious appellants' catalysts containing cesium or rubidium as the essential alkali metal (appealed claims 19 and 26, and claims depending therefrom). Without express comment, the board apparently tacitly adopted the examiner's reasons for rejection:

> [N]o *patentable distinction* was seen *in the claimed use of* cesium or rubidium rather than the sodium or potassium components taught by the patent. [Emphasis added.]

The reference to "patentable distinction," begs the inquiry under 35 U.S.C. §103. Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966).

[3] The only possible basis for rejecting appellants' catalyst composition claims requiring cesium or rubidium, not expressly described in McClellan, is the implicit assumption that the McClellan language "alkali metal" makes all elements of Group IA of the Periodic Table, lithium, sodium, potassium, rubidium, cesium and francium, equivalents for *modifying* bismuth molybdate *catalysts.* However, the known relationship of lithium, cesium, rubidium and francium to sodium and potassium, as Group IA elements, is not sufficient, in and of itself, to treat them as *interchangeable* in *catalyst* compositions. In re Doumani, 281 F.2d 215, 217, 126 USPQ 408, 410 (CCPA 1960).

Moreover, there is no description in McClellan which suggests the equivalency inferred by the PTO. The language "alkali metal" as used in McClellan relates to practical sources of contamination of the bismuth molybdate catalyst, by sodium or potassium salts of the *molybdate source* or by sodium in the carrier. In view of the lack of description in McClellan, or in any other art or record here, of cesium and/or rubidium reactants or catalytic components, McClellan's caveat concerning the effect of alkali metal contamination of catalysts, and the express limit on the amount of alkali metal tolerated by McClellan heat-treated catalysts, we conclude that the efficacy of the cesium- and rubidium-containing compositions as catalysts in claims 19-32 could only be derived from scrutiny of appellants' specification. Accordingly, the rejections of claims 19-21, 23, 25-28, and 30 are reversed.

V.

Turning to the issue of whether appellants have overcome the prima facie case of obvi-

stage of a two-stage calcination treatment may be undertaken at lower temperatures, 400° to 500°C, which can produce a catalyst, though a conventional one, and not McClellan's amorphous catalyst resulting from higher heat treatment, i.e., 750° to 850°C. McClellan does not state that sodium or potassium contamination of bismuth molybdate will not occur at 400-500°C.

ousness of claims 1-15, 18, 33 and 34 based on McClellan, we are faced with the question of what evidence must be considered. Appellants ask this court to consider all evidence in Friedrick I, II, III, and IV, as well as all other affidavit and declaration evidence of record. Appellants assert that the board erred in refusing to consider Friedrich III with respect to rejections based on McClellan alone. Friedrich III and Friedrich IV present rebuttal evidence relating to McClellan, as well as information and experiments responding to the board's criticisms of Friedrich II experiments relating to the Japanese patent.

Friedrich III and Friedrich IV, filed during the remand period after the first board decision, in which the rejections based on McClellan alone were affirmed, but before the second appeal, were ultimately entered as evidence by the Commissioner on equitable grounds, although the Commissioner acknowledged the examiner's reasons for refusing to enter the declarations; evidence therein related only to rejections already affirmed by the board in the first decisions.[14]
The examiner refused to consider the rebuttal evidence in Friedrich III and IV as it pertained to the rejections which were the subject of the first appeal, even after entry of the two declarations by the Commissioner, for the following reason:

Rule 198, however, does not authorize the Primary Examiner to consider matters already adjudicated, which Friedrich 111 [sic] declaration clearly attempts to force.

The board apparently adopted the examiner's reason without comment and expressly limited its second decision to consideration of the new rejections.

[4] Rule 198 proscriptions, relating to proceedings after the board's decision, are not relevant to a case remanded, as here, to the examiner by the board under Rule 196(d). Under rule 196(d), a board decision including a remand is "not * * * considered as a final decision in the case." Accordingly, under the express provisions of the rule, the board, after the remand proceedings, "shall * * * either adopt its decision as final *or* render a new decision on all of the claims on appeal." (Emphasis added.) Express PTO policy interpreting Rule 196(d) suggests that the decision containing the remand is not appealable under 35 U.S.C. §141. Manual of Patent Examining Procedure, §1213.04 (Oct. 8, 1981). Thus, it was error to apply Rule 198 in this instance.

All evidence presented by appellants should have been considered in connection with all rejections, and in view of the inordinate delays in these proceedings, we will proceed to do so.

Of most significance is the evidence in Friedrich III. By Friedrich III appellants sought to establish that appellants' four-component catalyst unexpectedly outperforms the composition of McClellan's Example 1 (modified to contain iron as a promoter). The experiment was made on the basis of appellant's catalyst containing sodium as the essential alkali metal component and activated at a temperature between 500° and 1250°F, in ammoxidation after 20 hours on stream to make acrylonitrile.

Initially, it is noted that appellants' process claims 1–5 are directed to isoprene production. Thus, the above comparison "in ammoxidation" is of no help with respect to overcoming the rejections of claims 1–5 and appellants do not so assert.

[5] It is well settled "that objective evidence or non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." In re Tiffin, 448 F.2d 791, 171 USPQ 294 (CCPA 1971). With respect to appellants' broad claims to a catalyst with "an alkali metal," the experiments detailed in Friedrich III, being limited to sodium only, are not commensurate in scope, and are, therefore, insufficient to rebut the prima facie case. No claim is directed to sodium as the essential alkali metal compo-

[14] In granting appellants' petition from the examiner's refusal to enter Friedrich III and IV declarations, the Commissioner stated:

> [1] It would be inequitable to deny applicants, who are the real parties of interest, as much right to participation and evidentiary showings [in Friedrich III and Friedrich IV] in their own reissue application as has already been accorded on the record to Protestor [by de facto entry and consideration of Rohm's declaration by Nemec, criticizing Friedrich III].
>
> * * *
>
> [2] It is noted that applicants, by virtue of filing a continuation reissue application, could formally introduce said declarations into the record, but with concommitant delays in ultimate resolution of the issues. It does not appear that such delay would serve any useful purpose. Furthermore, reference is again made to the already lengthy prosecution history of the instant case and the deferral of enforcement of the original patent as noted in Paper No. 89. Therefore, in view of the equities involved and in order to expedite the resolution of the issues in this case .... *The Primary Examiner is hereby directed to proceed* with dispatch as indicated in Paper No. 89 with the examination of the instant case including considering the Friedrich III and IV affidavits for their probative value and merit. [Emphasis added.]

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nent.[15] Accordingly, the rejections based on McClellan alone have not been overcome notwithstanding the evidence in Friedrich III.

However, the evidence in Table II of Friedrich II, rebuts any case of prima facie obviousness of claim 15. Claim 15 defines appellants' catalyst to be a composition of potassium, iron, bismuth, molybdenum, and cobalt. In Table II of Friedrich II, appellants have shown that a catalyst of claim 15 results in a percentage improvement (in yield) of 94% over their own catalyst of claims 6 and 7, containing potassium, iron, bismuth, and molybdenum (exclusive of cobalt) in acrolein production at 400°C, while at 310°C, the percentage improvement is even greater, 479%. In evaluating this evidence, we have noted that actual acrolein yields increase with increasing temperature.

[6] None of the prior art reviewed here, including McClellan, describes a catalyst more similar to that of claim 15 than those described in appellants' claims 6 or 7. Accordingly, that comparison in Table II of Friedrich II which shows that the claim 15 catalyst outperformed the others (i.e., claims 6 and 7) is evidence of unexpected superiority. This comparison, and the conclusion based thereon, is the ultimate extension of the "indirect showing of unexpected superiority" sanctioned by precedent. In re Fenn, 208 USPQ 470, 473 (CCPA 1981); In re Fouche, 439 F.2d 1237, 1241–42, 169 USPQ 429, 433 (CCPA 1971). Accordingly, the rejection of claim 15 based on McClellan is reversed.

VI.

The remainder of the rejections are those instituted by the board, pursuant to Rules 196(b) and 196(d). The grounds of rejections in the claim rejections are based on combinations of references. The grounds for the section 103 rejections under Rule 196(b) and 196(d) will be considered below, not necessarily in an order relating to the significance of the art to the rejected claims, but rather with respect to the number of claims affected thereby.

A.

Rejections Under 35 U.S.C. §103 Over Hiroki and Sennewald

The examiner refused to entertain the Rohm and Haas suggestion to reject claims over the combination of Sennewald (U.S. Patent No. 3,226,442) and Hiroki (U.S. Patent No. 3,346,617), stating:

> [S]uch a rejection would not be valid because there is insufficient basis for combining the Sennewald and Hiroki patents in the manner suggested.

However, in the board's first decision, the board added rejections of claims 6–8, 11, 16, 19, 23–26, 29, 30, and 32, over that combination and recommended similar rejections of allowed claims 17, 22, and 31. The board reasoned:

> We must disagree with the Examiner's view that these references are not properly combinable, because both are directed to catalytic compositions utilized in the production of methacrylonitrile from isobutylene.

[7] The utility of the two different catalysts of the Sennewald and Hiroki references might suggest, as the board purported, interchangeability of the catalysts. However, the express descriptions of those references which indicate that components of the two catalysts are not interchangeable is material to the validity of the rejection of catalyst composition claims under 35 U.S.C. §103.

In the board's limited discussion of this ground of rejection, the board concerned itself mainly with Hiroki without commenting on Sennewald, save for the Sennewald description of utility. Hiroki is directed to modifying a bismuth phosphomolybdate catalyst to improve the yields in ammoxidation processes

[15] We have considered, and dismiss, intervenor's criticisms of the reproduction of the McClellan catalyst in Friedrich III. The ultimate unsupportable extension of the Rohm and Haas position is that appellants should modify McClellan descriptions to make a "composite" which is appellants' invention. See discussion in In re Tiffin, 443 F.2d 394, 399-400, 170 USPQ 88, 93 (CCPA 1971), modified (as to claims 1-3 and 10-16) 448 F.2d 791, 171 USPQ 294 (CCPA 1971). Firstly, it was argued that the McClellan promoter should have been added prior to McClellan's critical calcination stage undertaken at 750° to 850°C. However, McClellan describes (in the generic teaching and in Example 1) undertaking catalyst calcination in two stages, the last stage at 750-850°C; and then describes calcination of the catalyst impregnated with promoter "at *any* desired temperature" (emphasis added). Accordingly, McClellan suggests three calcination stages. The lack of criticality in McClellan's own description of the temperature of the calcination of catalyst impregnated with promoter can hardly be construed to require a temperature of 750-850°C. Secondly, appellants are criticized for comparison of the two catalysts in ammoxidation; since McClellan expressly discloses use of McClellan catalysts in ammoxidation, an ammoxidation process is a reasonable reaction choice for comparative catalytic activity studies as to catalyst composition claims. Thirdly, intervenor criticizes the comparisons on the grounds that the compared catalysts selectivities are similar. This criticism would only have validity if the catalyst activity and resultant yields were similar, which is not the case here.

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by increasing the alkalinity of the bismuth phospho-molybdate catalyst. In the express words of Hiroki:

> [The bismuth phospho-molybdate catalyst] is made "more alkaline," either by the addition to the bismuth phospho-molybdate catalyst of an alkali metal or alkaline earth metal, or by the substitution of arsenic and/or antimony for a part or all of phosphorous in the phospho-molybdate composition, or further by the addition to the substantial molybdate of an oxide or hydroxide of an alkali or alkaline earth metal.

Hiroki, col. 2, lines 13–20.

Specifically, Hiroki suggests three, apparently equivalent, ways to increase the alkalinity of bismuth phospho-molybdate catalysts. The board treated those three ways of rendering the phospho-molybdate "more alkaline," as equivalent in making the rejection. This is not error as we find no description in Hiroki to indicate otherwise.

Hiroki was applied in the rejection for its suggestion to add alkali metal to a bismuth phospho-molybdate catalyst. Sennewald, silent with respect to alkali metal content, is combined with Hiroki for the Sennewald disclosure of iron addition to bismuth molybdate and to phospho-molybdate catalysts.

Sennewald characterized the improvements over prior catalysts to be based on the following differences "in the content of iron as an additional catalyst component and in the omission of such metals as tungsten, antimony and tin." Omission of antimony, as described by Sennewald, is inconsistent with the express object of Hiroki, to render the bismuth phospho-molybdate catalyst "more alkaline" by the addition of antimony and/or arsenic or its equivalent, the addition of alkali metal or alkaline earth metal.

The board's error, in rejecting claims over Hiroki and Sennewald, lies in its failure to recognize the express prohibition against inclusion of antimony in Sennewald's catalysts. In contrast, we have Hiroki's express statement as to interchangeability of alkali metal and antimony with the same beneficial result. Logical inquiry into the express statements of these two references would suggest lack of interchangeability of the respective catalytic components. Appellants' successful combination of alkali metal, iron, bismuth and molybdenum for a catalyst composition is contrary to these art descriptions.

Accordingly, we agree with the examiner's original conclusion and reverse the rejections under 35 U.S.C. §103 of claims 6–8, 11, 16–17, 19, 22–26, and 29–32 over Sennewald in combination with Hiroki.

B.

Rejections of Claims over Watanabe, Together with Other Evidence

In additional grounds of rejection, Watanabe was combined by the board with two other references, Yamaguchi, U.S. Patent No. 3,454,630, and Grasselli '631. Certain statements made by appellants with respect to Grasselli were treated as admissions, but these statements do not add information in addition to that of Grasselli '631 itself.

Turning to the substance of the rejections, the Watanabe catalyst systems discussed in section IV (composed of at least one oxide of tungsten, vanadium, molybdenum, uranium, copper, iron and chromium) differ significantly from those of Yamaguchi and Grasselli '631, each of which may require in combination, inter alia, iron, bismuth and molybdenum, and each of which differs from the other as to essential additional components. Specifically, Yamaguchi catalysts are oxides of iron, bismuth, phosphorus, molybdenum and nickel or cobalt or both nickel and cobalt, while Grasselli '631 embraces as one catalyst system an oxide system of iron, bismuth, molybdenum, and either nickel or a combination of iron and nickel optionally containing phosphorus, antimony, and tin.

Notwithstanding the Watanabe "suggestion" to use sodium or potassium as a promoter, which is the board's sole reason for reliance on Watanabe, we find no suggestion in Watanabe to look to the description embodied by Yamaguchi or Grasselli '631, or vice-versa, and we find no evidence suggesting interchangeability of Watanabe's catalyst compositions with those required by the other two references. Absent such suggestions, the description of Watanabe when viewed in terms of catalysts actually exemplified in the 22 examples, provides no reasonable basis for adding Watanabe's sodium or potassium to the combined oxides of iron, bismuth and molybdenum of Yamaguchi and Grasselli '631. In our view, the description of Watanabe, as a whole, would not provide the required reasonable expectation of successful addition of sodium or potassium to catalysts described in the two primary references. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Mercier, 515 F.2d 1161, 185 USPQ 774 (CCPA 1975).

C.

The Rejections Under Rule 196(b) and (d) of Claims 16, 17, 22, 24, 29 and 31

As noted in section II above, there are five different grounds of rejection of various

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groupings of these six claims. However, we find it necessary to discuss only McClellan taken with Grasselli '631, because of the descriptions of the catalysts or the references previously given.

To recapitulate, McClellan describes heat treatment (at 750° to 850°C) of bismuth molybdate, or bismuth phospho-molybdate, catalysts to render the crystalline structure amorphous, for use in oxydehydrogenations. McClellan, it was determined, suggests addition of iron to the basic catalyst. Moreover, it was determined that McClellan describes that those same catalysts will tolerate sodium or potassium ion impurities or contaminants to certain specified extents.

Grasselli '631 is directed to bismuth molybdate catalysts containing, in addition, the oxides of at least two transition metals, one of them being preferably iron, for use in oxydenydrogenations. Grasselli '631 is relied upon by the PTO for its description indicating that a portion of the bismuth in the base composition may be replaced by antimony, tin, copper, or arsenic. Grasselli '631 is silent with respect to the presence of alkali metal and describes a calcination temperature of above 500°F (about 262°C), which, according to Grasselli '631 Example 1, may be up to 800°F.

Appealed claim 16 requires the inclusion of antimony in appellants' catalyst containing potassium as the alkali metal. Moreover, appealed claim 16 embraces the inclusion of the second transition metal required by Grasselli '631. On the basis of the record before us, it is our view that a person of ordinary skill would have expected that inclusion of antimony, suggested by Grasselli '631, in the catalyst suggested by McClellan, would produce a composition operative as a catalyst, for example, in oxydehydrogenations.

Appealed claim 17 specifies potassium as the essential alkali metal and activation at 500°F (in air). Appellants argue that the temperature used by McClellan would destroy appellants' "activated catalytic oxide compound." In light of the description in both McClellan and Grasselli '631, more is necessary than appellants' argument with respect to the significance of appellants' temperature recitation. McClellan requires, as appellants point out, conversion of the crystalline composition to an amorphous form at 750–850°C. However, McClellan also indicates that heat treatment at a lower temperature can produce conventional catalysts, but in crystalline rather than the amorphous form which McClellan requires. The Grasselli '631 description concerning catalyst calcination temperatures is cumulative to McClellan's description concerning the effect of calcination temperature on the crystalline form of the composition. If appellants' catalysts, made at the temperature specified in claim 17, exhibit unobvious properties over that described by McClellan, there is no proof of that fact in this record.

Accordingly, we affirm the rejections of claims 16 and 17 over McClellan in view of Grasselli '631.

However, the rejections of claims 22, 24, 29, and 31 over McClellan and Grasselli '631 are reversed for reasons set forth above. These claims require the essential alkali metal component of appellants' catalyst composition to be cesium or rubidium. As discussed in section IV D, above, McClellan does not describe cesium or rubidium in catalyst compositions; and Grasselli, silent with respect to alkali metals, cannot change that determination.[16]

Accordingly, the rejections under 35 U.S.C. §103 of claims 15 and 19–32 are reversed, and rejections of claims 1–14, 16–18, 33 and 34 under 35 U.S.C. §103 are affirmed.

AFFIRMED IN PART AND REVERSED IN PART.

Court of Appeals, Federal Circuit

Kalman v. Kimberly-Clark Corporation

No. 83-540

Decided July 19, 1983

PATENTS

1. Court of Appeals for the Federal Circuit — Jursidiction (§26.55)

Federal Courts Improvement Act of 1982 Section 127(a), Pub. L. No. 97-164, 96 Stat, 25, gives CAFC exclusive jurisdiction of appeals from final decisions of federal district courts whose subject matter jurisdiction was based, in whole or in part, on 28 USC 1338(a), with exceptions.

2. Construction of specification and claims — Broad or narrow — In general (§22.101)

Construction of specification and claims — Comparison with other claims (§22.40)

Where some claims are broad and others narrow, narrow claim limitations cannot be read into broad whether to avoid invalidity or to escape infringement.

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[16] Similarly, neither the Japanese Patent (which describes potassium and sodium salts specifically,

Court of Appeals, Federal Circuit

Hodosh v. Block Drug Co., Inc.

No. 85-2607

Decided March 24, 1986

PATENTS

1. Patentability — Invention — Specific cases — Chemical (§51.5093)

Summary judgment holding that claimed tooth desensitizer was invalid for obviousness was improper, in view of existing questions of material fact concerning various terms used in Chinese and European references.

2. Patentability — Invention — In general (§51.501)

Secondary considerations and additional evidence likely to be considered at trial must be considered in obviousness determination.

Particular patents — Dental Treatments

3,863,006, Hodosh, Method for Desensitizing Teeth, holding of invalidity reversed.

Appeal from District Court for the District of New Jersey, Sarokin, J.; 226 USPQ 645.

Action by Milton Hodosh, and Richardson-Vicks, Inc., against Block Drug Company, Inc., and Dentco, Inc., for patent infringement. From summary judgment for defendants, plaintiffs appeal. Reversed and remanded.

John O. Tramontine, and Fish & Neave, and Hugh A. Chapin, and Kenyon & Kenyon, all of New York, N.Y. (W. Edward Bailey, Norman H. Beamer, Fish & Neave, Paul Lempel, William J. McNichol, and Kenyon & Kenyon, all of New York, N.Y., on the brief) for appellants.

Jerome G. Lee, and Morgan, Finnegan, Pine, Foley & Lee, both of New York, N.Y. (William S. Feiler, Maria C.H. Lin, Morgan, Finnegan, Pine, Foley & Lee, Marvin C. Soffen, Edward A. Meilman, and Ostrolenk, Faber, Gerb & Soffen, all of New York, N.Y., on the brief) for appellees.

Before Rich, Davis, and Baldwin, Circuit Judges.

Rich, Circuit Judge.

This appeal is from the July 12, 1985, judgment of the United States District Court for the District of New Jersey, 226 USPQ 645, granting summary judgment to Block Drug Company, Inc., et al. (Block) and holding that all six claims of patent No. 3,863,006 for "Method of Desensitizing Teeth" ('006 patent), issued to Dr. Milton Hodosh and licensed to Richardson-Vicks, Inc. (collectively, Hodosh), are invalid for obviousness under 35 USC 103. We reverse remand.

Background

Tooth desensitizers reduce discomfort and pain caused by tooth hypersensitivity or exposed dentin, the portion of the tooth between the enamel and the pulp which includes a myriad of microscopic tubules. Persons suffering from this condition react painfully to hot or cold foods, citric acid or sweets, or everyday chemical, thermal, or tactile stimuli including toothbrush contact.

Milton Hodosh, a practicing dentist for about thirty years, independently developed the claimed subject matter of the '006 patent and granted Richardson-Vicks an exclusive license to make, use, and sell the claimed invention; the latter markets its tooth desensitizing toothpaste under the trademark "Denquel."

Claim 1 of the '006 patent [1] reads:

> The method of desensitizing hypersensitive dentin and cementum by applying thereto an agent the essential ingredient of which is a nitrate of one of the following alkali metals: potassium, lithium or sodium said nitrate comprising between 1 percent and 20 percent by weight of said agent.

The remaining claims appear in the opinion below.

Appellee Block has, since 1961, marketed a tooth desensitizing toothpaste, covered by its patent No. 2,122,483 (the Rosenthal patent) for "Strontium Ion Toothpaste" issued in 1964, under the trademark "Sensodyne." The Rosenthal patent and the '006 patent disclose toothpaste formulae which are the same except that the latter contains, as a desensitizing agent, potassium nitrate instead of the Rosenthal-Block strontium chloride. After requesting and being denied a license under the '006 patent, Block developed its own potassium nitrate-containing tooth-desensitizing toothpaste called "Promise" and "Sensodyne-F." [2]

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[1] A certificate of reexamination confirming the patentability of claims 1-6 of the '006 patent was issued June 21, 1983, as a result of Hodosh's request for reexamination in 1982. Only one of the prior art references involved here, the Rosenthal patent, infra, was considered in the reexamination.

[2] Block also initiated regulatory proceedings designed to delay or prevent Richardson-Vicks' mar-

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strict of New Jersey, 226 USPQ
ng summary judgment to Block
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, are invalid for obviousness under
3. We reverse remand.

Background

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and the pulp which includes a
icroscopic tubules. Persons suffer-
s condition react painfully to hot or
citric acid or sweets, or everyday
ermal, or tactile stimuli including
ontact.
Hodosh, a practicing dentist for
years, independently developed
subject matter of the '006 patent
l Richardson-Vicks an exclusive
nake, use, and sell the claimed
ne latter markets its tooth desensi-
hpaste under the trademark

f the '006 patent [1] reads:
ethod of desensitizing hypersensi-
in and cementum by applying
agent the essential ingredient of
a nitrate of one of the following
als: potassium, lithium or sodium
te comprising between 1 percent
rcent by weight of said agent.
ing claims appear in the opinion

Block has, since 1961, marketed a
itizing toothpaste, covered by its
2,122,483 (the Rosenthal patent)
um Ion Toothpaste" issued in
the trademark "Sensodyne." The
atent and the '006 patent disclose
rmulae which are the same except
ter contains, as a desensitizing
sium nitrate instead of the Ro-
k strontium chloride. After re-
being denied a license under the
Block developed its own potas-
e-containing tooth-desensitizing
lled "Promise" and "Sensodyne-

te of reexamination confirming the
f claims 1-6 of the '006 patent was
, 1983, as a result of Hodosh's request
ion in 1982. Only one of the prior art
lved here, the Rosenthal patent, infra,
l in the reexamination.
initiated regulatory proceedings de-
or prevent Richardson-Vicks' mar-

March 30, 1983, Hodosh sued Block alleging that the sale of "Promise" and "Sensodyne-F" contributorily infringed and actively induced infringement of the '006 patent. Block answered and counterclaimed alleging patent misuse and consequent unenforceability of the '006 patent. On July 11, 1984, Block moved for summary judgment as to both misuse and patent invalidity. Oral argument was heard October 16, 1984, and decision was reserved. June 14, 1985, the reported decision was handed down granting the motion as to patent invalidity and dismissing the motion on misuse as moot, resulting in the judgment now on appeal.

The district court heard no expert testimony, but did hear arguments of counsel, receive briefs, review exhibits, and had before it declarations and affidavits from experts on both sides commenting on the eight prior art references involved here, including the Rosenthal patent. The court determined that there were no genuine issues of material fact and concluded as a matter of law that the claims of the '006 patent were invalid under §103 because the Rosenthal patent disclosed each element claimed in the '006 patent except the potassium nitrate, which, in its view, was disclosed in two Chinese references, both based on ancient Chinese writings. The court also stated that six European references supported its conclusion of obviousness.

Because the appropriateness of summary judgment is determined on an analysis of the facts, *First National Bank of Arizona* v. *Cities Service Co.*, 391 U.S. 253 (1968), and because everything about these references, as a whole, *see, e.g., Interconnect Planning Corp.* v. *Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547-48 (Fed. Cir. 1985), is important to our determination, we review the record and lay out the relevant portions of the references in some detail.

A. *The Chinese References*

1. *The Grand Dictionary of Chinese Medicine and Drugs*

(*The Grand Dictionary*)

The *Grand Dictionary*, published in Hong Kong in 1963 and written in Chinese, is based on ancient Chinese compilations assembled roughly 500 years ago from works of physicians going back 4000-5000 years. Only a portion of the 1963 Chinese text was before the court and is before us on appeal. For purposes of this litigation, that portion was translated into English by Block's translator, Roger Wei-Ming Tsao (Mr. Cao). Mr. Cao is a doctor of Chinese medicine and a bilingual tutor. Block's other expert, Dr. Stephen Wei, a professor of dentistry fluent in Chinese, concurred in that translation. The writings from which the *Grand Dictionary* was compiled are not in evidence nor are any earlier writings.

In a nutshell, the district court relied upon the *Grand Dictionary* because of its discussion of "xiao shi" to which the Grand Dictionary associates the name "niter" and the chemical composition KNO_3 and the ability to cure, inter alia, tooth pain. The court's opinion was that this reference teaches the use of xiao shi, which is the same as niter and is therefore the same as potassium nitrate, to cure tooth pain; thus, the teachings of the Rosenthal patent and the *Grand Dictionary* show that the '006 invention would have been obvious.

The following discussion and quotations are part of an attempt to convey the nature of the *Grand Dictionary*. The translated portion of the *Grand Dictionary* is entitled "Niter." The text under the first subheading "Nomenclature" reads: "It was so named because it has the power to consume various stones." Under "Other Names Stated in Classical Medical Books," the text reads "Mang Xiao (Bie-Lu), Bitter Xiao (Zhen-Quan), Flaming Xiao (Tu-Su) . . . and Xiao-Shi . . . ." Thereafter, following "Foreign Names," the *Grand Dictionary* reads: "Salpetrae, Salnitri (in Latin); Niter (in English); and Salpoter (in German)." One page later, "KNO_3" is listed under "Chemical Composition."

The portion upon which Block and the district court rely to show that this substance cures tooth pain is headed "Collective Statements" and reads:

> (Ming): Li-Shi-Zhen said: It cures summer infections and the catching of colds. It cures acute enteritis with severe vomiting, exertion through excessive sexual activity, black jaundice, chronic abdominal pain, conjunctivitis, headaches and tooth pain.

The next three or so pages of the *Grand Dictionary* list the ailments that this substance cures. An interesting but not atypical paragraph reads: "For curing the paralysis of the four limbs, leprosy or problems caused by Taoist stone eating." This substance also apparently cures indigestion, lack of energy, typhoid, cataracts, and much, much more. The *Grand Dictionary* compares what appears to

keting of "Denquel." Block, having allegedly failed to comply with Food and Drug Administration (FDA) procedures before marketing "Promise" and "Sensodyne-F" in competitive response to Richardson-Vicks' introduction of "Denquel," is currently defending itself in forfeiture proceedings initiated by the FDA.

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be various forms in which xiao shi is found, and the characteristics of each. An excerpt is:

> Pu-Xiao (Na_2SO_4) has the nature of water, tastes salty, and its flavor is cold. It can only descend and cannot ascend. It is Yin within Yin — that's why it can cleanse the accumulation in the gastrointestinal tract and can expel the San-Jiao devilish fire. Whereas Niter (KNO3) has the nature of fire, tastes bitter and spicy, tastes slightly salty and has a flavor which is very warm, it's [sic] nature is ascending. It is fire within water. That's why it can break the accumulation and disperse hardness, and cure the febrile diseases.

2. *Ben Cao Gang Mu*

Ben Cao Gang Mu (*Ben Cao*) is a treatise on Chinese Medicine published in Hong Kong, in Chinese, in 1930, 1954, and 1965, but was originally written by Li-Shi-Zhen who lived during the Ming Dynasty.[3] Like the *Grand Dictionary*, only a portion of the Chinese text *Ben Cao* is in evidence and that portion was translated by Mr. Cao and Dr. Wei for purposes of this litigation. The district court relied upon *Ben Cao* because it discusses "xiao shi," which the translation of *Ben Cao* states is "niter" and associates the ability to cure "tooth pain (Ya Tong or Ya Teng)."

It is important to note, and the district court appeared to accept as fact, that the portion of the *Grand Dictionary* relied upon was compiled during the Ming Dynasty of the 13th to 15th centuries in *Ben Cao Gang Mu* so that the relevant portion of the *Grand Dictionary* is substantially a restatement of *Ben Cao* with some modification by an unidentified author. The court stated that these two references "quote the same Ming Dynasty source as labeling KNO_3 for tooth pain."

The *Ben Cao* translation is entitled "Xiao-Shi (Niter)" and refers to the same "Other names" for this substance listed in the *Grand Dictionary*. With respect to the quoted sections above, the *Ben Cao* translation is nearly verbatim. It has this to say about tooth pain:

> Da Ming states: It cures summer infections and the catching of colds, acute enteritis with severe vomiting, exertion thru excessive sexual activity and black jaundice, chronic abdominal pain, conjunctivitis, headache and tooth pain (Ya-Tong or Ya Teng).

Hodosh argues that summary judgment was inappropriate; issues of fact as to the meanings of xiao shi and ya tong remain because a skilled dental researcher would surely seek and obtain a complete translation of the *Grand Dictionary* and of the other ancient Chinese references and would read those references carefully. Hodosh also argues that the ancient references should be dismissed because a person skilled in the art would find them incredible and would regard them as a quagmire of medical and dental nonsense. It therefore takes issue with the court's holding quoted below which apparently precluded inquiry into the accuracy of the references by one skilled in the art:

> [A]ttacks upon the translation leading up to the prior art reference embodied in the *Grand Dictionary of Chinese Medicine and Drugs*, . . . or upon Chinese medicine as a whole, . . . are not here regarded as particularly pertinent, since they require skill beyond the scope of the "experienced researcher in dental fields . . . ."

Hodosh relies heavily on its expert's, Dr. Shklar's, testimony about the Chinese references: "[T]hey represent in modern terms, materials that are rarely comprehensible and frequently contradictory in their literal terms. The materials are largely seen by contemporary medical scientists as absurd; no serious medical researcher would waste his or her time with them."[4] Hodosh also contests this holding by the district court:

> Nor, if it is true that KNO_3 alleviates tooth sensitivity, is such reference in the prior art rebutted by the existence of errors in the reference such as, for example, the claim that KNO_3 is a cure for "exertion through excessive sexual activity." Whatever the merits of the other aspects of the Chinese references, the fact that they reveal KNO_3 to be a cure for ya tong is what is dispositive here. The reference clearly discloses such function of potassium nitrate, albeit in the context of otherwise incredible, and even erroneous descriptions of the compound's quality.

With respect to the specific meaning of xiao shi as used in these references, both Dr. Shklar and Hodosh's other expert, Mr. Yen, a professional translator of Chinese and English lan-

[3] The Ming Dynasty (1368-1644 AD) was marked by the restoration of traditional institutions in China and the development of the arts, especially in porcelain, textiles, and painting.

[4] Dr. Shklar is the Charles A. Brackett Professor of Oral Pathology at the Harvard School of Dental Medicine, and is an acclaimed expert in dentistry. He is also an expert on the history of dentistry and holds membership in the American Academy of the History of Dentistry.

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guages, stated that the compiler of the *Grand Dictionary* erred in associating potassium nitrate or niter with xiao shi. Mr. Yen states that he

> was not able to render one single precise version because various dictionaries contain different and even conflicting definitions. For example, *Source of Words*, a Chinese language dictionary, published by Commercial Press, Taiwan, which has editions dating back to 1915, defines "Xiao-Shi" as "Mang-Xiao" on page 1255, and under "Mang-Xiao" on page 1770, reference is made that "Mang-Xiao" is "Liu-Suen-Na," and on page 1523 "Liu-Suen-Na" is defined as sodium sulfate ($Na_2SO_410H_2O$).

Mr. Yen also stated that "Xiao-Shi could be more than one material and that more than one material may be represented by the term 'Xiao-Shi'."

Dr. Shklar concurred:

> In my opinion, therefore, the answer to the question: What was "Xiao-Shi," is that it represented many different materials which cannot be identified with certainty.
>
> * * *
>
> Thus, these Exhibits did not describe potassium nitrate to one skilled in the art any more than any of the hundreds of salts, ores and oxides that possess some of the enumerated properties.

In addition, Dr. Shklar stated: "It is insufficient to simply state, as the Block translator does, that 'Xiao-Shi' is 'niter,' and then cite a modern dictionary to 'establish' that 'niter' is potassium nitrate." With respect to both the *Grand Dictionary* and *Ben Cao*, he stated that "the translator appears to have inserted the term 'niter' into the text where the phrase 'consumer of stones' actually belongs."

Block's arguments, on the other hand, in part based on the short affidavit by Mr. Wei, substantially follow the district court's opinion. Block also challenges the competence of Hodosh's experts stating that they "either had no knowledge or training in the Chinese language or Chinese medicine or were unfamiliar with dentistry or medicine generally." Block also emphasizes that the Chinese references correctly disclose many of potassium nitrate's characteristics, like burning with a violet flame, useability for making signal fires and gun powder, and its water solubility; these three properties of xiao shi in the Chinese references definitely confirm, according to Block, that xiao shi is potassium nitrate, KNO_3.

B. *The European Prior Art*

This art is contained in six references and was not relied upon to any significant degree by Block or the district court. Hodosh scarcely mentions it on appeal, instead preferring to show the existence of genuine issues of material fact with respect to the Chinese references. After concluding that using potassium nitrate to cure tooth pain would have been obvious from Rosenthal in view of the Chinese art, the court stated: "Such holding is strengthened by the European prior art which, while ambiguous because of the several conflicting definitions in the term 'niter,' at least suggest to one skilled in the art that potassium nitrate ought to be tried as a cure for tooth pain in general."

Block submitted no affidavits that addressed the substance of the European references. Hodosh's Dr. Shklar, on the other hand, stated why this art, part of the "humors, spirits and Alchemy of the Dark Ages" having whatever medicinal effect they did by virtue of their use of wine, opium, or other narcotic substances, would have been questioned by one skilled in the art. He specifically contends that Block's translation of "nitre" is erroneous: "it is common knowledge that these terms meant sodium carbonate and/or sodium carbonate-sodium bicarbonate mixture. . . ."

To afford a glimpse of the nature of these references, an interesting and typical excerpt, one quoted by the district court, based upon a statement by the long since deceased French surgeon Guy de Chauliac reads that "a mixture of 'cuttlebone, small white sea shells, pumice, burnt stag's horn, *nitre*, alum, rock salt, burnt roots of iris, aristolochia, and reeds' could create an effective dentifrice." (District court's emphasis.) Three of the European references are based on that statement. The district court noted the others:

> Additionally, a 1693 treatise by the British Professor of Physics William Salmon states that nitrum "held in the Mouth . . . immediately helps the Toothach, if burnt and used in a Dentifrice, it cleanses and whitens the Teeth." . . . Similarly, a reference work by Hardianus a Mynsicht, translated into English in 1682, describes a mixture, including "nitre" as a "tincture for the toothache." . . . Finally, Pliny the Elder, in his *Historie of the World, The Second Tome*, translated into English in 1601, describes the use of nitre to "easeth the toothach, if the mouth and gums be washed therwith," or if burned, as a dentifrice. [Reference to Exhibits omitted.]

With this description of both the Chinese and European references, and of what they represent as a whole, in hand, we consider the proper application of the *Graham* standards and their effect upon the propriety of summary judgment in this case. *See generally Graham* v. *John Deere Co.*, 383 U.S. 1, 17 [148 USPQ 459, 467] (1966); *Panduit Corp.* v. *Dennison*

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Manufacturing Co., 774 F.2d 1082, 227 USPQ 337 (Fed. Cir. 1985).

OPINION

A. *Summary Judgment*

Summary judgment, in patent as in other cases, is appropriate where there is no genuine issue of material fact, and the movant is entitled to judgment as a matter of law. *See Molinaro* v. *Fannon/Courier Corp.* 745 F.2d 651, 653-54, 223 USPQ 706, 707 (Fed. Cir. 1984). The movant bears the burden of demonstrating the absence of all genuine issues of material fact, and the district court must view the evidence in a light most favorable to the nonmoving party and draw all reasonable inferences in its favor. *See United States* v. *Diebold, Inc.*, 369 U.S. 654, 655 (1962); *Palumbo* v. *Don-Joy Co.*, 762 F.2d 969, 973, 226 USPQ 5, 7 (Fed. Cir. 1985). The party opposing summary judgment must show an evidentiary conflict on the record; mere denials or conclusory statements are not sufficient. *Barmag Barmer Maschinenfabrik AG* v. *Murata Machinery, Ltd.*, 731 F.2d 831, 836, 221 USPQ 561, 564 (Fed. Cir. 1984). Summary judgment is authorized where it is quite clear what the truth is. *Sartor* v. *Arkansas Natural Gas Corp.*, 321 U.S. 620, 627 (1944).

B. *The Issues Below*

The decision and opinion of the district court granting summary judgment dealt with two issues: the first was whether the '006 patent is invalid as anticipated under §102(b), the court holding it is not; and the second was whether the '006 patent is invalid for obviousness under §103, the court holding that it is. Hodosh of course appeals the summary judgment with respect to only the issue on which it lost — obviousness and Block has not appealed. Because we are remanding for trial, however, we will comment briefly on anticipation to make it clear that we deem that question to have been conclusively disposed of in this case and because it is closely related to the obviousness issue.

1. *Anticipation, §102(b)*

We agree entirely with the district court's holding that the '006 patent is not invalid as anticipated because there is no issue of fact that none of the prior art references discloses every element of the claimed invention. This issue was, therefore, appropriately and properly disposed of by summary judgment.

We do not agree, however, with some of the district court's remarks about anticipation, in particular, that the unavailability of the Chinese references and whether one skilled in the art could locate them with "reasonable diligence" bears on whether those references anticipate the claimed subject matter. Whether a reference is available as prior art and whether it anticipates (i.e., contains every claimed element) are separate questions. Moreover, the district court's determination that the references are unavailable for §102 purposes seems to be inconsistent with the approach subsequently taken by the district court in determining obviousness. The court later used these same references to support its holding that the claimed subject matter would have been obvious at the time the invention was made to one of ordinary skill in the art.

2. *Obviousness, §103*

[1] Questions of material fact remain with respect to the meaning of various terms used in the Chinese and European references and we therefore hold that summary judgment on the ground of obviousness of the claimed invention was improper.

The district court's statement that ya tong means tooth hypersensitivity as well as tooth pain is the resolution of a head-on factual controversy. The court improperly drew the inference against Hodosh, the nonmoving party, that a statement about ya tong made to the German Patent Office by Dr. Hodosh's German patent agent was made with knowledge of the Chinese references. The statement in question occurred seven years after the '006 patent issued in connection with Dr. Hodosh's counterpart German application. The statement was: "The supersensitivity of dentine has been known for a long time and can be traced back 4000 years to the Chinese where it was known as 'Ya Tong'." Hodosh in this suit disclaims this statement urging that it was factual error.

There is no evidence that the above statement was based on the Chinese references or that Dr. Hodosh conveyed this information to the German patent agent. The important fact question as to the meaning of ya tong cannot be overcome simply by styling this statement an admission binding on Hodosh. Hodosh is entitled, as Block essentially concedes, to rebut the statement with evidence to the contrary. Hodosh will have that chance at trial.

Nor does the statement in the affidavit of Block's expert, Dr. Wei, that ya tong means tooth hypersensitivity eliminate the presence of the question of the meaning of ya tong. As the Supreme Court long ago observed, "Ex-

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perience has shown that opposite opinions of persons professing to be experts, may be obtained to any amount. . . ." *Winans* v. *New York and Erie Railroad Co.*, 62 U.S. 88 (1859). The substance of Dr. Skhlar's affidavit on behalf of Hodosh goes far beyond merely denying that ya tong means tooth hypersensitivity and thus is more than adequate to show an evidentiary conflict on the record with respect to this crucial point, thus precluding summary judgment. *Cf. Union Carbide Corp.* v. *American Can* Co., 724 F.2d 1567, 1571, 220 USPQ 584, 587-88 (Fed. Cir. 1984).

Furthermore, a genuine issue of material fact exists with respect to the meaning of the terms nitre, nitrum, and nitri as used in the European references. Dr. Sklhar's affidavit is more than adequate to withstand the challenge of this summary judgment motion. A reasonable inference that these terms are sodium, as opposed to potassium, compounds is permissible; Hodosh has shown an evidentiary conflict on the record. The European references, Dr. Sklhar explained in his affidavit, are based on the 77 A.D. writings of Pliny The Elder, who understood these terms to mean "sodium carbonate and/or a sodium carbonate-sodium bicarbonate mixture."

The obviousness determination here, given the existence of genuine material issues of fact with respect to the meanings of terms used in these references, is not suitably disposed of by summary judgment under the rules pertaining thereto. *See generally Palumbo*, supra, and *Lemelson* v. *TRW, Inc.*, 760 F.2d 1254, 1260-61, 225 USPQ 697, 700-01 (Fed. Cir. 1985). The fact issues herein must be resolved by trial in which the conflicting views of the experts will be subject to the refining fire of cross examination, a more effective means of arriving at the legal conclusion of obviousness vel non than perusal of ex parte affidavits and declarations of partisan experts lobbed at each other from opposing trenches.

We observe, for the benefit of the trial court, that we are totally unimpressed by Block's forensic device of comparing the Rosenthal prior art toothpaste formula and the Hodosh toothpaste example in parallel columns and then asserting, as though it were filled with significant meaning, that the "only difference is the use of potassium nitrate in place of strontium chloride," or that "the Hodosh patent merely substitutes potassium nitrate for strontium chloride." This device was pushed to the limit in oral argument by pointing out that the Hodosh toothpaste has the *same* formula, *except* for the active desensitizing ingredient, down to the last decimal point. This argument is meaningless on the obviousness issue. "Sensodyne" and apparently other desensitizing toothpaste formulae being well known as commercial products, it is entirely clear that Dr. Hodosh's invention was the discovery of an apparently superior *desensitizing agent* and he never thought it was a toothpaste formula. He made that invention even if it should later be decided that it was known to the Chinese. It is apparent that Hodosh's patent solicitor merely adopted the prior art Rosenthal toothpaste base formula as a convenient example to illustrate the kind of a paste in which the Hodosh desensitizer might be used, which was within his right. The similarities — indeed, identity — of the paste bases is irrelevant in considering the issue of the unobviousness of the desensitizer. The Rosenthal patent, cited as prior art by Hodosh in his patent specification, was the jumping-off place for the description of his discovery. Hodosh does not claim to have been the first inventor of a desensitizing toothpaste; he claims to have improved it. The issue for trial is whether his improvement would have been obvious.[5]

C. *Secondary Considerations*

The district court refused on the motion for summary judgment to consider the evidence of secondary considerations. After acknowledging its existence and the arguments based on it, it stated:

[5] Our comments on the district court's obviousness determination generally include the following tenets of patent law that must be adhered to when applying §103: (1) the claimed invention must be considered as a whole (35 USC 103; *see, e.g., Jones* v. *Hardy*, 727 F.2d 1524, 1529, 220 USPQ 1021, 1024 (Fed. Cir. 1984) (though the difference between claimed invention and prior art may seem slight, it may also have been the key to advancement of the art)); (2) the references must be considered as a whole and suggest the desirability and thus the obviousness of making the combination (*see, e.g., Lindemann Maschinenfabrik GmbH* v. *American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984); (3) the references must be viewed without the benefit of hindsight vision afforded by the claimed invention (*e.g., W.L. Gore & Associates, Inc.* v. *Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983)); (4) "ought to be tried" is not the standard with which obviousness is determined (*Jones*, supra, 727 F.2d at 1530, 220 USPQ at 1026); and (5) the presumption of validity remains constant and intact throughout litigation (35 USC 285; *e.g., American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359-60, 220 USPQ 763, 770 (Fed. Cir. 1984)).

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However, the court continues to find that the Hodosh patent is invalid on grounds of obviousness; these secondary considerations stem not from the novelty or inventiveness engendered by substituting potassium nitrate in an already existing formula, but from a lack of knowledge on the part of those in the field of the references here cited. That lack is here overcome by the presumption of omniscience discussed, *supra*, a rule of law by which the court is bound, whatever its merits.

[2] That secondary considerations are not considered unless there is evidence that those in the industry knew of the prior art is a non sequitur. Evidence of secondary considerations is considered independently of what any real person *knows* about the prior art. These considerations are *objective* criteria of obviousness that help illuminate the subjective determination involved in the hypothesis used to draw the legal conclusion of obviousness based upon the first three factual inquiries delineated in *Graham*. Thus, to require that actual inventors in the field have the omniscience of the hypothetical person in the art is not only contrary to case law, *see Kimberly-Clark* v. *Johnson & Johnson*, 745 F.2d 1437, 223 USPQ 603 (Fed. Cir. 1984), but eliminates a useful tool for trial judges faced with a nonobviousness determination.

The secondary consideration evidence of record and the additional evidence likely to be submitted at trial must be considered in the obviousness determination. *See generally Fromson* v. *Advance Offset Plate, Inc.*, 755 F.2d 1549, 1557, 225 USPQ 26, 32 (Fed. Cir. 1985).

Conclusion

The grant of summary judgment of invalidity is *reversed* and the case is *remanded* for trial in accordance with this opinion.

REVERSED AND REMANDED

Court of Appeals, Federal Circuit

Witco Chemical Corporation v. Peachtree Doors, Inc., et al.

Nos. 85-972 and 85-1453

Decided March 24, 1986

PATENTS

1. Pleading and practice in courts — Jury trial — Validity and infringement (§53.577)

New trial on all issues is warranted in patent infringement action in which jury, after deciding validity and enforceability issues and having reached impasse on infringement issue, was excused for six weeks and was then recalled and provided with additional instructions, since such actions seemingly coerced jury into reaching its infringement verdict, and since partial retrial would be inappropriate.

Particular patents — Foams

3,846,347, Satterly, Rigid Foams from Polyurethane and Methods and Compositions for Use in their Preparation, holding of infringement vacated.

4,248,975, Satterly, Rigid Insulating Polyurethane Foam, holding of infringement vacated.

Appeal from District Court for the Northern District of Georgia, Hall, J.

Action by Witco Chemical Corporation, against Peachtree Doors, Inc., and Mobay Chemical Corporation, for patent infringement and breach of contract, in which defendants counterclaim for patent invalidity and unenforceability. From judgment for plaintiffs in part and from decision denying defendants' motions for mistrial or for new trial, defendants appeal. Judgment vacated and remanded for new trial.

Maurice B. Stiefel, and Stiefel, Gross, Kurland & Pavane, both of New York, N.Y. (Marc S. Gross and Ralph R. Palo, both of New York, N.Y., and James A. Quinton, John S. Pratt, and Kilpatrick & Cody, both of Atlanta, Ga., on the brief) for appellants.

Harold Haidt, and Brooks, Haidt, Haffner & Delahunty, both of New York, N.Y. (G.T. Delahunty and Charles G. Mueller, both of New York, N.Y., and A. Felton, Jenkins, Jr., Bruce W. Baber, and King & Spalding, all of Atlanta, Ga., on the brief) for appellee.

Before Davis, Smith and Bissell, Circuit Judges.

Bissell, Circuit Judge.

This is an appeal from the judgment, after a jury trial, entered on December 4, 1984, amended December 10, 1984, by the United States District Court for the Northern District of Georgia, holding Witco Chemical Corporation's (Witco) U.S. Patent Nos. 3,846,347 ('347) and 4,248,975 ('975) (collectively called Witco's patents) not invalid and infringed by foam-forming systems and prepolymers sold by Mobay Chemical Corporation (Mobay)

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KSR International Co. v. Teleflex Inc.

U.S. Supreme Court
No. 04-1350
Decided April 30, 2007

PATENTS

[1] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Rigid application of "teaching, suggestion, or motivation" test, under which patent claim is proved obvious only if prior art, nature of problem addressed by inventor, or knowledge of person having ordinary skill in art reveals some motivation or suggestion to combine prior art teachings, is inconsistent with expansive and flexible "functional approach" to resolution of obviousness issue, under which scope and content of prior art are determined, differences between prior art and claims at issue are ascertained, level of ordinary skill in pertinent art is resolved, and secondary considerations such as commercial success, long felt but unsolved needs, and failure of others may be considered if doing so would prove instructive; rigid TSM approach is therefore rejected.

[2] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Patentability/Validity — Obviousness — Evidence of (§ 115.0906)

Variations of particular work available in one field of endeavor may be prompted by design incentives and other market forces, either in same field or different one, and if person of ordinary skill in art can implement predictable variation, 35 U.S.C. § 103 likely bars its patentability; similarly, if particular technique has been used to improve one device, and person of ordinary skill would recognize that it would improve similar devices in same way, then using that technique is obvious unless its actual application is beyond person's skill, and court resolving obviousness issue therefore must ask whether improvement is more than predictable use of prior art elements according to their established functions.

[3] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Patentability/Validity — Obviousness — Evidence of (§ 115.0906)

Court determining whether claimed combination of elements known in prior art would have been obvious will often be required to look to interrelated teachings of multiple patents, effects of demands known to design community or present in marketplace, and background knowledge of person of ordinary skill in art in order to determine whether there was apparent reason to combine known elements in manner claimed in patent in suit, and in order to facilitate review, this analysis should be made explicit; however, such analysis need not seek out precise teachings directed to specific subject matter of challenged claim, since court can take account of inferences and creative steps that person of ordinary skill in art would employ.

[4] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Idea underlying "teaching, suggestion, or motivation" test, under which patent claim is proved obvious only if prior art, nature of problem addressed by inventor, or knowledge of person having ordinary skill in art reveals some motivation or suggestion to combine prior art teachings, is not necessarily inconsistent with expansive and flexible "functional approach" to resolution of obviousness issue, since TSM test is based on helpful insights, namely, that patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in prior art, and that it can be important to identify reason that would have prompted person of ordinary skill in art to combine elements in manner claimed by new invention; however, it is error to apply TSM test as rigid and mandatory formula that limits obviousness analysis through formalistic conception of words "teaching," "suggestion," and "motivation," or by overemphasis on importance of published articles and explicit content of issued patents, since market demand, rather than scientific literature, often drives design trends, and granting patent protection to advances that would occur "in the ordinary course" without real innovation retards progress and may, in case of patents

combining previously known elements, deprive prior inventions of their value or utility.

[5] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Narrow conception of obviousness inquiry, reflected in appellate court's application of "teaching, suggestion, or motivation" test, resulted in erroneous conclusion that summary judgment of obviousness should be vacated, since decision was based on erroneous holding that courts and patent examiners should look only to problem that patentee was trying to solve, and on erroneous assumption that person of ordinary skill in art attempting to solve problem will be led only to those elements of prior art designed to solve same problem, since court erroneously concluded that patent claim cannot be proved obvious merely by showing that combination of elements was "obvious to try," and since appellate court drew wrong conclusion from risk of courts and patent examiners falling prey to "hindsight" bias, in that rigid application of preventative rules that deny fact finders recourse to common sense are neither necessary nor consistent with precedent.

[6] Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Patentability/Validity — Obviousness — Evidence of (§ 115.0906)

Fact that claimed combination of elements was "obvious to try" might show that such combination was obvious under 35 U.S.C. § 103, since, if there is design need or market pressure to solve problem, and there are finite number of identified, predictable solutions, person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation.

[7] Patentability/Validity — Obviousness — Relevant prior art — Particular inventions (§ 115.0903.03)

Patentability/Validity — Obviousness — Combining references (§ 115.0905)

Asserted claim of patent for position-adjustable vehicle pedal assembly having electronic pedal-position sensor attached to fixed pivot point is invalid as obvious over combination of prior art references, since prior art patent discloses support structure for adjustable pedal assembly in which one pivot point stays fixed, since, at relevant time, marketplace had created strong incentive to convert mechanical pedals to those employing electronic sensors, and pedal designer of ordinary skill would have seen benefit in upgrading device of prior patent with sensor required by new engines using computer-controlled throttles, since other prior art references taught utility of placing sensor on pedal's support structure rather than on footpad, and on nonmoving part of pedal structure, since most obvious nonmoving point on structure from which sensor can easily detect pedal position is fixed pivot point, and since designer seeking to avoid wire-chafing problems with electronic adjustable pedals would have known to employ adjustable pedal with fixed pivot disclosed by prior art patent; declaration submitted by patentees does not indicate that device of prior patent was so flawed that there was no reason to upgrade it to be compatible with modern engines, and patentees have shown no secondary considerations to dislodge obviousness determination.

[8] Patentability/Validity — Obviousness — Evidence of (§ 115.0906)

JUDICIAL PRACTICE AND PROCEDURE

Procedure — Summary judgment — Patents (§ 410.3303)

Procedure — Evidence — Expert testimony (§ 410.3703)

Party's submission of conclusory expert affidavit addressing issue of obviousness in patent action does not preclude summary judgment, even though federal district court can and should take into account expert testimony, which may resolve or keep open certain questions of fact, since ultimate judgment of obviousness is legal determination; in present case, in which content of prior art, scope of asserted claim, and level of ordinary skill in art were not in material dispute, and obviousness of claim was apparent from these factors, summary judgment was appropriate, and nothing in declarations proffered by patentees prevented district court from reaching conclusions underlying its order for summary judgment of obviousness.

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Particular patents — General and mechanical — Vehicle control pedal assembly

6,237,565, Engelgau, adjustable pedal assembly with electronic throttle control, invalid for obviousness.

On writ of certiorari to the U.S. Court of Appeals for the Federal Circuit, Schall, J.

Action by Teleflex Inc. and Technology Holding Co. against KSR International Co. for patent infringement. The U.S. District Court for the Eastern District of Michigan granted summary judgment in favor of defendant on ground that patent in suit was invalid for obviousness, and plaintiffs appealed. Grant of summary judgment was vacated and remanded, and defendant-appellee filed petition for writ of certiorari. Reversed and remanded.

James W. Dabney, New York, N.Y.; Stephen S. Rabinowitz, Henry C. Lebowitz, Mitchell E. Epner, and Darcy M. Goddard, of Fried, Frank, Harris, Shriver & Jacobson, New York; John F. Duffy, of Fried, Frank, Harris, Shriver & Jacobson, Washington, D.C., for petitioner.

Thomas C. Goldstein, Michael A. O'Shea, Garreth A. Sarosi, Christopher R. Pudelski, and Sarah C. Rispin, of Akin Gump Strauss Hauer & Feld, Washington; Kenneth C. Bass III and Robert G. Sterne, of Sterne, Kessler, Goldstein & Fox, Washington; Rodger D. Young, Steven Susser, and David Poirier, of Young & Susser, Southfield, Mich.; Samuel J. Haidle and David M. LaPrairie, of Howard & Howard, Bloomfield Hills, Mich.; Tracy L. Casadio and Elizabeth H. Rader, of Akin Gump Strauss Hauer & Feld, Los Angeles, Calif., for respondent.

Syllabus by the Court.

To control a conventional automobile's speed, the driver depresses or releases the gas pedal, which interacts with the throttle via a cable or other mechanical link. Because the pedal's position in the footwell normally cannot be adjusted, a driver wishing to be closer or farther from it must either reposition himself in the seat or move the seat, both of which can be imperfect solutions for smaller drivers in cars with deep footwells. This prompted inventors to design and patent pedals that could be adjusted to change their locations. The Asano patent reveals a support structure whereby, when the pedal location is adjusted, one of the pedal's pivot points stays fixed. Asano is also designed so that the force necessary to depress the pedal is the same regardless of location adjustments. The Redding patent reveals a different, sliding mechanism where both the pedal and the pivot point are adjusted.

In newer cars, computer-controlled throttles do not operate through force transferred from the pedal by a mechanical link, but open and close valves in response to electronic signals. For the computer to know what is happening with the pedal, an electronic sensor must translate the mechanical operation into digital data. Inventors had obtained a number of patents for such sensors. The so-called '936 patent taught that it was preferable to detect the pedal's position in the pedal mechanism, not in the engine, so the patent disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. The Smith patent taught that to prevent the wires connecting the sensor to the computer from chafing and wearing out, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad. Inventors had also patented self-contained modular sensors, which can be taken off the shelf and attached to any mechanical pedal to allow it to function with a computer-controlled throttle. The '068 patent disclosed one such sensor. Chevrolet also manufactured trucks using modular sensors attached to the pedal support bracket, adjacent to the pedal and engaged with the pivot shaft about which the pedal rotates. Other patents disclose electronic sensors attached to adjustable pedal assemblies. For example, the Rixon patent locates the sensor in the pedal footpad, but is known for wire chafing.

After petitioner KSR developed an adjustable pedal system for cars with cable-actuated throttles and obtained its '976 patent for the design, General Motors Corporation (GMC) chose KSR to supply adjustable pedal systems for trucks using computer-controlled throttles. To make the '976 pedal compatible with the trucks, KSR added a modular sensor to its design. Respondents (Teleflex) hold the exclusive license for the Engelgau patent, claim 4 of which discloses a position-adjustable pedal assembly with an electronic pedal position sensor attached at a fixed pivot point. Despite having denied a similar, broader claim, the

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U.S. Patent and Trademark Office (PTO) had allowed claim 4 because it included the limitation of a fixed pivot position, which distinguished the design from Redding's. Asano was neither included among the Engelgau patent's prior art references nor mentioned in the patent's prosecution, and the PTO did not have before it an adjustable pedal with a fixed pivot point. After learning of KSR's design for GMC, Teleflex sued for infringement, asserting that KSR's pedal system infringed the Engelgau patent's claim 4. KSR countered that claim 4 was invalid under § 103 of the Patent Act, which forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."

Graham v. *John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 [148 USPQ 459], set out an objective analysis for applying § 103: "[T]he scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." While the sequence of these questions might be reordered in any particular case, the factors define the controlling inquiry. However, seeking to resolve the obviousness question with more uniformity and consistency, the Federal Circuit has employed a "teaching, suggestion, or motivation" (TSM) test, under which a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person having ordinary skill in the art reveals some motivation or suggestion to combine the prior art teachings.

The District Court granted KSR summary judgment. After reviewing pedal design history, the Engelgau patent's scope, and the relevant prior art, the court considered claim 4's validity, applying *Graham*'s framework to determine whether under summary-judgment standards KSR had demonstrated that claim 4 was obvious. The court found "little difference" between the prior art's teachings and claim 4: Asano taught everything contained in the claim except using a sensor to detect the pedal's position and transmit it to a computer controlling the throttle. That additional aspect was revealed in, *e.g.*, the '068 patent and Chevrolet's sensors. The court then held that KSR satisfied the TSM test, reasoning (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to Rixon's chafing problems by positioning the sensor on the pedal's fixed structure, which could lead to the combination of a pedal like Asano with a pedal position sensor.

Reversing, the Federal Circuit ruled the District Court had not applied the TSM test strictly enough, having failed to make findings as to the specific understanding or principle within a skilled artisan's knowledge that would have motivated one with no knowledge of the invention to attach an electronic control to the Asano assembly's support bracket. The Court of Appeals held that the District Court's recourse to the nature of the problem to be solved was insufficient because, unless the prior art references addressed the precise problem that the patentee was trying to solve, the problem would not motivate an inventor to look at those references. The appeals court found that the Asano pedal was designed to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted, whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal. The Rixon pedal, said the court, suffered from chafing but was not designed to solve that problem and taught nothing helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals and did not necessarily go to the issue of motivation to attach the electronic control on the pedal assembly's support bracket. So interpreted, the court held, the patents would not have led a person of ordinary skill to put a sensor on an Asano-like pedal. That it might have been obvious to try that combination was likewise irrelevant. Finally, the court held that genuine issues of material fact precluded summary judgment.

Held: The Federal Circuit addressed the obviousness question in a narrow, rigid manner that is inconsistent with § 103 and this Court's precedents. KSR provided convincing evidence that mounting an available sensor on a

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fixed pivot point of the Asano pedal was a design step well within the grasp of a person of ordinary skill in the relevant art and that the benefit of doing so would be obvious. Its arguments, and the record, demonstrate that the Engelgau patent's claim 4 is obvious. Pp. 11–24.

1. *Graham* provided an expansive and flexible approach to the obviousness question that is inconsistent with the way the Federal Circuit applied its TSM test here. Neither § 103's enactment nor *Graham*'s analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. See *Great Atlantic & Pacific Tea Co.* v. *Supermarket Equipment Corp.*, 340 U.S. 147, 152 [87 USPQ 303]. Such a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. See, *e.g.*, *United States* v. *Adams*, 383 U.S. 39, 50–52 [148 USPQ 479]. When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions. Following these principles may be difficult if the claimed subject matter involves more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ. Pp. 11–14.

(b) The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. Helpful insights, however, need not become rigid and mandatory formulas. If it is so applied, the TSM test is incompatible with this Court's precedents. The diversity of inventive pursuits and of modern technology counsels against confining the obviousness analysis by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasizing the importance of published articles and the explicit content of issued patents. In many fields there may be little discussion of obvious techniques or combinations, and market demand, rather than scientific literature, may often drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, for patents combining previously known elements, deprive prior inventions of their value or utility. Since the TSM test was devised, the Federal Circuit doubtless has applied it in accord with these principles in many cases. There is no necessary inconsistency between the test and the *Graham* analysis. But a court errs where, as here, it transforms general principle into a rigid rule limiting the obviousness inquiry. Pp. 14–15.

(c) The flaws in the Federal Circuit's analysis relate mostly to its narrow conception of the obviousness inquiry consequent in its application of the TSM test. The Circuit first erred in holding that courts and patent examiners should look only to the problem the patentee was trying to solve. Under the correct analysis, any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the

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manner claimed. Second, the appeals court erred in assuming that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to solve the same problem. The court wrongly concluded that because Asano's primary purpose was solving the constant ratio problem, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. It is common sense that familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle. Regardless of Asano's primary purpose, it provided an obvious example of an adjustable pedal with a fixed pivot point, and the prior art was replete with patents indicating that such a point was an ideal mount for a sensor. Third, the court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Finally, the court drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. Rigid preventative rules that deny recourse to common sense are neither necessary under, nor consistent with, this Court's case law. Pp. 15–18.

2. Application of the foregoing standards demonstrates that claim 4 is obvious. Pp. 18–23.

(a) The Court rejects Teleflex's argument that the Asano pivot mechanism's design prevents its combination with a sensor in the manner claim 4 describes. This argument was not raised before the District Court, and it is unclear whether it was raised before the Federal Circuit. Given the significance of the District Court's finding that combining Asano with a pivot-mounted pedal position sensor fell within claim 4's scope, it is apparent that Teleflex would have made clearer challenges if it intended to preserve this claim. Its failure to clearly raise the argument, and the appeals court's silence on the issue, lead this Court to accept the District Court's conclusion. Pp. 18–20.

(b) The District Court correctly concluded that when Engelgau designed the claim 4 subject matter, it was obvious to a person of ordinary skill in the art to combine Asano with a pivot-mounted pedal position sensor. There then was a marketplace creating a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for doing so. The Federal Circuit considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a modular sensor similar to the ones used in the Chevrolet trucks and disclosed in the '068 patent. The proper question was whether a pedal designer of ordinary skill in the art, facing the wide range of needs created by developments in the field, would have seen an obvious benefit to upgrading Asano with a sensor. For such a designer starting with Asano, the question was where to attach the sensor. The '936 patent taught the utility of putting the sensor on the pedal device. Smith, in turn, explained not to put the sensor on the pedal footpad, but instead on the structure. And from Rixon's known wire-chafing problems, and Smith's teaching that the pedal assemblies must not precipitate any motion in the connecting wires, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious such point is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor there. Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Teleflex has not shown anything in the prior art that taught away from the use of Asano, nor any secondary factors to dislodge the determination that claim 4 is obvious. Pp. 20–23.

3. The Court disagrees with the Federal Circuit's holding that genuine issues of material fact precluded summary judgment. The ultimate judgment of obviousness is a legal determination. *Graham*, 383 U.S., at 17. Where, as here, the prior art's content, the patent claim's scope, and the level of ordinary skill in the art are not in material dispute and the claim's ob-

viousness is apparent, sum
appropriate. P. 23.

119 Fed. Appx. 282, reve
manded.

KENNEDY, J., delivered the
unanimous Court.

Kennedy, J.

Teleflex Incorporated a
Technology Holding Compa
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Company for patent infring
at issue, United States Pate
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With Electronic Throttle
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Claim 4 of the Engelgau
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are such that the subject m
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pertains."

In *Graham* v. *John Deer*
City, 383 U.S. 1 [148 USPQ
Court set out a framework
statutory language of § 103
based on the logic of the e
Hotchkiss v. *Greenwood*, 11
and its progeny. See 383 U.
analysis is objective:

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prior art are to be determ
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sue are to be ascertained;
ordinary skill in the pertir
Against this background th
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termined. Such secondary
commercial success, long

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viousness is apparent, summary judgment is appropriate. P. 23.

119 Fed. Appx. 282, reversed and remanded.

KENNEDY, J., delivered the opinion for a unanimous Court.

Kennedy, J.

Teleflex Incorporated and its subsidiary Technology Holding Company—both referred to here as Teleflex—sued KSR International Company for patent infringement. The patent at issue, United States Patent No. 6,237,565 B1, is entitled "Adjustable Pedal Assembly With Electronic Throttle Control." Supplemental App. 1. The patentee is Steven J. Engelgau, and the patent is referred to as "the Engelgau patent." Teleflex holds the exclusive license to the patent.

Claim 4 of the Engelgau patent describes a mechanism for combining an electronic sensor with an adjustable automobile pedal so the pedal's position can be transmitted to a computer that controls the throttle in the vehicle's engine. When Teleflex accused KSR of infringing the Engelgau patent by adding an electronic sensor to one of KSR's previously designed pedals, KSR countered that claim 4 was invalid under the Patent Act, 35 U.S.C. § 103, because its subject matter was obvious.

Section 103 forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."

In *Graham* v. *John Deere Co. of Kansas City*, 383 U.S. 1 [148 USPQ 459] (1966), the Court set out a framework for applying the statutory language of § 103, language itself based on the logic of the earlier decision in *Hotchkiss* v. *Greenwood*, 11 How. 248 (1851), and its progeny. See 383 U.S., at 15–17. The analysis is objective:

> "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.*, at 17–18.

While the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls. If a court, or patent examiner, conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under § 103.

Seeking to resolve the question of obviousness with more uniformity and consistency, the Court of Appeals for the Federal Circuit has employed an approach referred to by the parties as the "teaching, suggestion, or motivation" test (TSM test), under which a patent claim is only proved obvious if "some motivation or suggestion to combine the prior art teachings" can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art. See, *e.g.*, *Al-Site Corp.* v. *VSI Int'l, Inc.*, 174 F.3d 1308, 1323–1324 [50 USPQ2d 1161] (CA Fed. 1999). KSR challenges that test, or at least its application in this case. See 119 Fed. Appx. 282, 286–290 (CA Fed. 2005). Because the Court of Appeals addressed the question of obviousness in a manner contrary to § 103 and our precedents, we granted certiorari, 547 U.S. ___ (2006). We now reverse.

I

A

In car engines without computer-controlled throttles, the accelerator pedal interacts with the throttle via cable or other mechanical link. The pedal arm acts as a lever rotating around a pivot point. In a cable-actuated throttle control the rotation caused by pushing down the pedal pulls a cable, which in turn pulls open valves in the carburetor or fuel injection unit. The wider the valves open, the more fuel and air are released, causing combustion to increase and the car to accelerate. When the driver takes his foot off the pedal, the opposite occurs as the cable is released and the valves slide closed.

In the 1990's it became more common to install computers in cars to control engine operation. Computer-controlled throttles open and close valves in response to electronic signals, not through force transferred from the pedal by a mechanical link. Constant, delicate

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adjustments of air and fuel mixture are possible. The computer's rapid processing of factors beyond the pedal's position improves fuel efficiency and engine performance.

For a computer-controlled throttle to respond to a driver's operation of the car, the computer must know what is happening with the pedal. A cable or mechanical link does not suffice for this purpose; at some point, an electronic sensor is necessary to translate the mechanical operation into digital data the computer can understand.

Before discussing sensors further we turn to the mechanical design of the pedal itself. In the traditional design a pedal can be pushed down or released but cannot have its position in the footwell adjusted by sliding the pedal forward or back. As a result, a driver who wishes to be closer or farther from the pedal must either reposition himself in the driver's seat or move the seat in some way. In cars with deep footwells these are imperfect solutions for drivers of smaller stature. To solve the problem, inventors, beginning in the 1970's, designed pedals that could be adjusted to change their location in the footwell. Important for this case are two adjustable pedals disclosed in U.S. Patent Nos. 5,010,782 (filed July 28, 1989) (Asano) and 5,460,061 (filed Sept. 17, 1993) (Redding). The Asano patent reveals a support structure that houses the pedal so that even when the pedal location is adjusted relative to the driver, one of the pedal's pivot points stays fixed. The pedal is also designed so that the force necessary to push the pedal down is the same regardless of adjustments to its location. The Redding patent reveals a different, sliding mechanism where both the pedal and the pivot point are adjusted.

We return to sensors. Well before Engelgau applied for his challenged patent, some inventors had obtained patents involving electronic pedal sensors for computer-controlled throttles. These inventions, such as the device disclosed in U.S. Patent No. 5,241,936 (filed Sept. 9, 1991) ('936), taught that it was preferable to detect the pedal's position in the pedal assembly, not in the engine. The '936 patent disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. U.S. Patent No. 5,063,811 (filed July 9, 1990) (Smith) taught that to prevent the wires connecting the sensor to the computer from chafing and wearing out, and to avoid grime and damage from the driver's foot, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad.

In addition to patents for pedals with integrated sensors inventors obtained patents for self-contained modular sensors. A modular sensor is designed independently of a given pedal so that it can be taken off the shelf and attached to mechanical pedals of various sorts, enabling the pedals to be used in automobiles with computer-controlled throttles. One such sensor was disclosed in U.S. Patent No. 5,385,068 (filed Dec. 18, 1992) ('068). In 1994, Chevrolet manufactured a line of trucks using modular sensors "attached to the pedal support bracket, adjacent to the pedal and engaged with the pivot shaft about which the pedal rotates in operation." 298 F.Supp.2d 581, 589 (ED Mich. 2003).

The prior art contained patents involving the placement of sensors on adjustable pedals as well. For example, U.S. Patent No. 5,819,593 (filed Aug. 17, 1995) (Rixon) discloses an adjustable pedal assembly with an electronic sensor for detecting the pedal's position. In the Rixon pedal the sensor is located in the pedal footpad. The Rixon pedal was known to suffer from wire chafing when the pedal was depressed and released.

This short account of pedal and sensor technology leads to the instant case.

B

KSR, a Canadian company, manufactures and supplies auto parts, including pedal systems. Ford Motor Company hired KSR in 1998 to supply an adjustable pedal system for various lines of automobiles with cable-actuated throttle controls. KSR developed an adjustable mechanical pedal for Ford and obtained U.S. Patent No. 6,151,976 (filed July 16, 1999) ('976) for the design. In 2000, KSR was chosen by General Motors Corporation (GMC or GM) to supply adjustable pedal systems for Chevrolet and GMC light trucks that used engines with computer-controlled throttles. To make the '976 pedal compatible with the trucks, KSR merely took that design and added a modular sensor.

Teleflex is a rival to KSR in the design and manufacture of adjustable pedals. As noted, it is the exclusive licensee of the Engelgau patent. Engelgau filed the patent application on August 22, 2000 as a continuation of a pre-

vious application for 6,109,241, which was file 1999. He has sworn he in subject matter on February gelgau patent discloses a tronic pedal described in th "simplified vehicle contr that is less expensive, and parts and is easier to pack hicle." Engelgau, col. 2, mental App. 6. Claim 4 of here, describes:

> "A vehicle control ped prising:
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> a support adapted to be hicle structure;
>
> an adjustable pedal as pedal arm moveable in f tions with respect to saic
>
> a pivot for pivotally supp able pedal assembly wi support and defining a pi
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> an electronic control att port for controlling a vel
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> said apparatus character tronic control being resp for providing a signal t pedal arm position as sai about said pivot axis be plied positions wherein t pivot remains constant w moves in fore and aft spect to said pivot." *Id.*, Supplemental App. 8 omitted).

We agree with the Distri claim discloses "a positio assembly with an electror sensor attached to the supp pedal assembly. Attaching support member allows the in a fixed position while the pedal." 298 F.Supp.2d, at 5

Before issuing the Engelg Patent and Trademark Offi one of the patent claims th but broader than the pres claim did not include the re sensor be placed on a fixe PTO concluded the claim combination of the prior art ding and Smith, explaining:

vious application for U.S. Patent No. 6,109,241, which was filed on January 26, 1999. He has sworn he invented the patent's subject matter on February 14, 1998. The Engelgau patent discloses an adjustable electronic pedal described in the specification as a "simplified vehicle control pedal assembly that is less expensive, and which uses fewer parts and is easier to package within the vehicle." Engelgau, col. 2, lines 2–5, Supplemental App. 6. Claim 4 of the patent, at issue here, describes:

> "A vehicle control pedal apparatus comprising:
>
> a support adapted to be mounted to a vehicle structure;
>
> an adjustable pedal assembly having a pedal arm moveable in for[e] and aft directions with respect to said support;
>
> a pivot for pivotally supporting said adjustable pedal assembly with respect to said support and defining a pivot axis; and
>
> an electronic control attached to said support for controlling a vehicle system;
>
> said apparatus characterized by said electronic control being responsive to said pivot for providing a signal that corresponds to pedal arm position as said pedal arm pivots about said pivot axis between rest and applied positions wherein the position of said pivot remains constant while said pedal arm moves in fore and aft directions with respect to said pivot." *Id.*, col. 6, lines 17–36, Supplemental App. 8 (diagram numbers omitted).

We agree with the District Court that the claim discloses "a position-adjustable pedal assembly with an electronic pedal position sensor attached to the support member of the pedal assembly. Attaching the sensor to the support member allows the sensor to remain in a fixed position while the driver adjusts the pedal." 298 F.Supp.2d, at 586–587.

Before issuing the Engelgau patent the U.S. Patent and Trademark Office (PTO) rejected one of the patent claims that was similar to, but broader than, the present claim 4. The claim did not include the requirement that the sensor be placed on a fixed pivot point. The PTO concluded the claim was an obvious combination of the prior art disclosed in Redding and Smith, explaining:

> " 'Since the prior ar[t] references are from the field of endeavor, the purpose disclosed . . . would have been recognized in the pertinent art of Redding. Therefore it would have been obvious . . . to provide the device of Redding with the . . . means attached to a support member as taught by Smith.' " *Id.*, at 595.

In other words Redding provided an example of an adjustable pedal and Smith explained how to mount a sensor on a pedal's support structure, and the rejected patent claim merely put these two teachings together.

Although the broader claim was rejected, claim 4 was later allowed because it included the limitation of a fixed pivot point, which distinguished the design from Redding's. *Ibid.* Engelgau had not included Asano among the prior art references, and Asano was not mentioned in the patent's prosecution. Thus, the PTO did not have before it an adjustable pedal with a fixed pivot point. The patent issued on May 29, 2001 and was assigned to Teleflex.

Upon learning of KSR's design for GM, Teleflex sent a warning letter informing KSR that its proposal would violate the Engelgau patent. " 'Teleflex believes that any supplier of a product that combines an adjustable pedal with an electronic throttle control necessarily employs technology covered by one or more' " of Teleflex's patents. *Id.*, at 585. KSR refused to enter a royalty arrangement with Teleflex; so Teleflex sued for infringement, asserting KSR's pedal infringed the Engelgau patent and two other patents. *Ibid.* Teleflex later abandoned its claims regarding the other patents and dedicated the patents to the public. The remaining contention was that KSR's pedal system for GM infringed claim 4 of the Engelgau patent. Teleflex has not argued that the other three claims of the patent are infringed by KSR's pedal, nor has Teleflex argued that the mechanical adjustable pedal designed by KSR for Ford infringed any of its patents.

C

The District Court granted summary judgment in KSR's favor. After reviewing the pertinent history of pedal design, the scope of the Engelgau patent, and the relevant prior art, the court considered the validity of the contested claim. By direction of 35 U.S.C. § 282, an issued patent is presumed valid. The District Court applied *Graham*'s framework to deter-

mine whether under summary-judgment standards KSR had overcome the presumption and demonstrated that claim 4 was obvious in light of the prior art in existence when the claimed subject matter was invented. See § 102(a).

The District Court determined, in light of the expert testimony and the parties' stipulations, that the level of ordinary skill in pedal design was " 'an undergraduate degree in mechanical engineering (or an equivalent amount of industry experience) [and] familiarity with pedal control systems for vehicles.' " 298 F.Supp.2d, at 590. The court then set forth the relevant prior art, including the patents and pedal designs described above.

Following *Graham*'s direction, the court compared the teachings of the prior art to the claims of Engelgau. It found "little difference." 298 F.Supp.2d, at 590. Asano taught everything contained in claim 4 except the use of a sensor to detect the pedal's position and transmit it to the computer controlling the throttle. That additional aspect was revealed in sources such as the '068 patent and the sensors used by Chevrolet.

Under the controlling cases from the Court of Appeals for the Federal Circuit, however, the District Court was not permitted to stop there. The court was required also to apply the TSM test. The District Court held KSR had satisfied the test. It reasoned (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to the wire chafing problems in Rixon, namely locating the sensor on the fixed structure of the pedal. This could lead to the combination of Asano, or a pedal like it, with a pedal position sensor.

The conclusion that the Engelgau design was obvious was supported, in the District Court's view, by the PTO's rejection of the broader version of claim 4. Had Engelgau included Asano in his patent application, it reasoned, the PTO would have found claim 4 to be an obvious combination of Asano and Smith, as it had found the broader version an obvious combination of Redding and Smith. As a final matter, the District Court held that the secondary factor of Teleflex's commercial success with pedals based on Engelgau's design did not alter its conclusion. The District Court granted summary judgment for KSR.

With principal reliance on the TSM test, the Court of Appeals reversed. It ruled the District Court had not been strict enough in applying the test, having failed to make " 'finding[s] as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the] invention' . . . to attach an electronic control to the support bracket of the Asano assembly." 119 Fed. Appx., at 288 (brackets in original) (quoting *In re Kotzab*, 217 F.3d 1365, 1371 [55 USPQ2d 1313] (CA Fed. 2000)). The Court of Appeals held that the District Court was incorrect that the nature of the problem to be solved satisfied this requirement because unless the "prior art references address[ed] the precise problem that the patentee was trying to solve," the problem would not motivate an inventor to look at those references. 119 Fed. Appx., at 288.

Here, the Court of Appeals found, the Asano pedal was designed to solve the " 'constant ratio problem' "—that is, to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted—whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal. *Ibid.* As for Rixon, the court explained, that pedal suffered from the problem of wire chafing but was not designed to solve it. In the court's view Rixon did not teach anything helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals and did not "necessarily go to the issue of motivation to attach the electronic control on the support bracket of the pedal assembly." *Ibid.* When the patents were interpreted in this way, the Court of Appeals held, they would not have led a person of ordinary skill to put a sensor on the sort of pedal described in Asano.

That it might have been obvious to try the combination of Asano and a sensor was likewise irrelevant, in the court's view, because " ' "[o]bvious to try" has long been held not to constitute obviousness.' " *Id.*, at 289 (quoting *In re Deuel*, 51 F.3d 1552, 1559 [34 USPQ2d 1210] (CA Fed. 1995)).

The Court of Appeals also faulted the District Court's consideration of the PTO's rejection of the broader version of claim 4. The District Court's role, the Court of Appeals explained, was not to speculate regarding what the PTO might have done had the Engelgau patent mentioned Asano. Rather, the court held, the District Court was obliged first to

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The Court of Appeals further held that genuine issues of material fact precluded summary judgment. Teleflex had proffered statements from one expert that claim 4 " 'was a simple, elegant, and novel combination of features,' " 119 Fed. Appx., at 290, compared to Rixon, and from another expert that claim 4 was nonobvious because, unlike in Rixon, the sensor was mounted on the support bracket rather than the pedal itself. This evidence, the court concluded, sufficed to require a trial.

II

A

[1] We begin by rejecting the rigid approach of the Court of Appeals. Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here. To be sure, *Graham* recognized the need for "uniformity and definiteness." 383 U.S., at 18. Yet the principles laid down in *Graham* reaffirmed the "functional approach" of *Hotchkiss*, 11 How. 248. See 383 U.S., at 12. To this end, *Graham* set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive. *Id.*, at 17.

Neither the enactment of § 103 nor the analysis in *Graham* disturbed this Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. For over a half century, the Court has held that a "patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men." *Great Atlantic & Pacific Tea Co.* v. *Supermarket Equipment Corp.*, 340 U.S. 147, 152 [87 USPQ 303] (1950). This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. Three cases decided after *Graham* illustrate the application of this doctrine.

In *United States* v. *Adams*, 383 U.S. 39, 40 [148 USPQ 479] (1966), a companion case to *Graham*, the Court considered the obviousness of a "wet battery" that varied from prior designs in two ways: It contained water, rather than the acids conventionally employed in storage batteries; and its electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. 383 U.S., at 50–51. It nevertheless rejected the Government's claim that Adams's battery was obvious. The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *Id.*, at 51–52. When Adams designed his battery, the prior art warned that risks were involved in using the types of electrodes he employed. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art.

In *Anderson's-Black Rock, Inc.* v. *Pavement Salvage Co.*, 396 U.S. 57 [163 USPQ 673] (1969), the Court elaborated on this approach. The subject matter of the patent before the Court was a device combining two preexisting elements: a radiant-heat burner and a paving machine. The device, the Court concluded, did not create some new synergy: The radiant-heat burner functioned just as a burner was expected to function; and the paving machine did the same. The two in combination did no more than they would in separate, sequential operation. *Id.*, at 60–62. In those circumstances, "while the combination of old elements performed a useful function, it added nothing to the nature and quality of the radiant-heat burner already patented," and the patent failed under § 103. *Id.*, at 62 (footnote omitted).

Finally, in *Sakraida* v. *AG Pro, Inc.*, 425 U.S. 273 [189 USPQ 449] (1976), the Court derived from the precedents the conclusion that when a patent "simply arranges old elements with each performing the same function it had been known to perform" and yields no

more than one would expect from such an arrangement, the combination is obvious. *Id.*, at 282.

[2] The principles underlying these cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock*, are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

[3] Following these principles may be more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 [78 USPQ2d 1329] (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

B

[4] When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel*, 292 F.2d 955, 956–957 [130 USPQ 206] (1961). As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

In the years since the Court of Customs and Patent Appeals set forth the essence of the TSM test, the Court of Appeals no doubt has applied the test in accord with these principles in many cases. There is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis. But when a court transforms the general principle into a

rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.

C

The flaws in the analysis of the Court of Appeals relate for the most part to the court's narrow conception of the obviousness inquiry reflected in its application of the TSM test. In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

[5] The first error of the Court of Appeals in this case was to foreclose this reasoning by holding that courts and patent examiners should look only to the problem the patentee was trying to solve. 119 Fed. Appx., at 288. The Court of Appeals failed to recognize that the problem motivating the patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

The second error of the Court of Appeals lay in its assumption that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem. *Ibid.* The primary purpose of Asano was solving the constant ratio problem; so, the court concluded, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. *Ibid.* Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle. Regardless of Asano's primary purpose, the design provided an obvious example of an adjustable pedal with a fixed pivot point; and the prior art was replete with patents indicating that a fixed pivot point was an ideal mount for a sensor. The idea that a designer hoping to make an adjustable electronic pedal would ignore Asano because Asano was designed to solve the constant ratio problem makes little sense. A person of ordinary skill is also a person of ordinary creativity, not an automaton.

[6] The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." *Id.*, at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

The Court of Appeals, finally, drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to " 'guard against slipping into the use of hindsight' " (quoting *Monroe Auto Equipment Co.* v. *Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 [141 USPQ 549] (CA6 1964))). Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it.

We note the Court of Appeals has since elaborated a broader conception of the TSM test than was applied in the instant matter. See, *e.g.*, *DyStar Textilfarben GmbH & Co. Deutschland KG* v. *C. H. Patrick Co.*, 464 F.3d 1356, 1367 [80 USPQ2d 1641] (2006) ("Our suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense"); *Alza Corp.* v. *Mylan Labs., Inc.*, 464 F.3d 1286, 1291 [80 USPQ2d 1001] (2006) ("There is flexibility in our obviousness jurisprudence because a motivation may be found *implicitly* in the prior art. We do not

have a rigid test that requires an actual teaching to combine ..."). Those decisions, of course, are not now before us and do not correct the errors of law made by the Court of Appeals in this case. The extent to which they may describe an analysis more consistent with our earlier precedents and our decision here is a matter for the Court of Appeals to consider in its future cases. What we hold is that the fundamental misunderstandings identified above led the Court of Appeals in this case to apply a test inconsistent with our patent law decisions.

III

When we apply the standards we have explained to the instant facts, claim 4 must be found obvious. We agree with and adopt the District Court's recitation of the relevant prior art and its determination of the level of ordinary skill in the field. As did the District Court, we see little difference between the teachings of Asano and Smith and the adjustable electronic pedal disclosed in claim 4 of the Engelgau patent. A person having ordinary skill in the art could have combined Asano with a pedal position sensor in a fashion encompassed by claim 4, and would have seen the benefits of doing so.

A

Teleflex argues in passing that the Asano pedal cannot be combined with a sensor in the manner described by claim 4 because of the design of Asano's pivot mechanisms. See Brief for Respondents 48–49, and n. 17. Therefore, Teleflex reasons, even if adding a sensor to Asano was obvious, that does not establish that claim 4 encompasses obvious subject matter. This argument was not, however, raised before the District Court. There Teleflex was content to assert only that the problem motivating the invention claimed by the Engelgau patent would not lead to the solution of combining of Asano with a sensor. See Teleflex's Response to KSR's Motion for Summary Judgment of Invalidity in No. 02–74586 (ED Mich.), pp. 18–20, App. 144a–146a. It is also unclear whether the current argument was raised before the Court of Appeals, where Teleflex advanced the nonspecific, conclusory contention that combining Asano with a sensor would not satisfy the limitations of claim 4. See Brief for Plaintiffs-Appellants in No. 04–1152 (CA Fed.), pp. 42–44. Teleflex's own expert declarations, moreover, do not support the point Teleflex now raises. See Declaration of Clark J. Radcliffe, Ph.D., Supplemental App. 204–207; Declaration of Timothy L. Andresen, *id.*, at 208–210. The only statement in either declaration that might bear on the argument is found in the Radcliffe declaration:

> "Asano . . . and Rixon . . . are complex mechanical linkage-based devices that are expensive to produce and assemble and difficult to package. It is exactly these difficulties with prior art designs that [Engelgau] resolves. The use of an adjustable pedal with a single pivot reflecting pedal position combined with an electronic control mounted between the support and the adjustment assembly at that pivot was a simple, elegant, and novel combination of features in the Engelgau '565 patent." *Id.*, at 206, ¶16.

Read in the context of the declaration as a whole this is best interpreted to mean that Asano could not be used to solve "[t]he problem addressed by Engelgau '565[:] to provide a less expensive, more quickly assembled, and smaller package adjustable pedal assembly with electronic control." *Id.*, at 205, ¶10.

The District Court found that combining Asano with a pivot-mounted pedal position sensor fell within the scope of claim 4. 298 F.Supp.2d, at 592–593. Given the sigificance of that finding to the District Court's judgment, it is apparent that Teleflex would have made clearer challenges to it if it intended to preserve this claim. In light of Teleflex's failure to raise the argument in a clear fashion, and the silence of the Court of Appeals on the issue, we take the District Court's conclusion on the point to be correct.

B

[7] The District Court was correct to conclude that, as of the time Engelgau designed the subject matter in claim 4, it was obvious to a person of ordinary skill to combine Asano with a pivot-mounted pedal position sensor. There then existed a marketplace that created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for achieving this advance. The Court of Appeals considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a

modular sensor similar to the ones used in the Chevrolet truckline and disclosed in the '068 patent. The District Court employed this narrow inquiry as well, though it reached the correct result nevertheless. The proper question to have asked was whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, would have seen a benefit to upgrading Asano with a sensor.

In automotive design, as in many other fields, the interaction of multiple components means that changing one component often requires the others to be modified as well. Technological developments made it clear that engines using computer-controlled throttles would become standard. As a result, designers might have decided to design new pedals from scratch; but they also would have had reason to make pre-existing pedals work with the new engines. Indeed, upgrading its own pre-existing model led KSR to design the pedal now accused of infringing the Engelgau patent.

For a designer starting with Asano, the question was where to attach the sensor. The consequent legal question, then, is whether a pedal designer of ordinary skill starting with Asano would have found it obvious to put the sensor on a fixed pivot point. The prior art discussed above leads us to the conclusion that attaching the sensor where both KSR and Engelgau put it would have been obvious to a person of ordinary skill.

The '936 patent taught the utility of putting the sensor on the pedal device, not in the engine. Smith, in turn, explained to put the sensor not on the pedal's footpad but instead on its support structure. And from the known wire-chafing problems of Rixon, and Smith's teaching that "the pedal assemblies must not precipitate any motion in the connecting wires," Smith, col. 1, lines 35–37, Supplemental App. 274, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious nonmoving point on the structure from which a sensor can easily detect the pedal's position is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor on a pivot, thereby designing an adjustable electronic pedal covered by claim 4.

Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Following similar steps to those just explained, a designer would learn from Smith to avoid sensor movement and would come, thereby, to Asano because Asano disclosed an adjustable pedal with a fixed pivot.

Teleflex indirectly argues that the prior art taught away from attaching a sensor to Asano because Asano in its view is bulky, complex, and expensive. The only evidence Teleflex marshals in support of this argument, however, is the Radcliffe declaration, which merely indicates that Asano would not have solved Engelgau's goal of making a small, simple, and inexpensive pedal. What the declaration does not indicate is that Asano was somehow so flawed that there was no reason to upgrade it, or pedals like it, to be compatible with modern engines. Indeed, Teleflex's own declarations refute this conclusion. Dr. Radcliffe states that Rixon suffered from the same bulk and complexity as did Asano. See *id.*, at 206. Teleflex's other expert, however, explained that Rixon was itself designed by adding a sensor to a pre-existing mechanical pedal. See *id.*, at 209. If Rixon's base pedal was not too flawed to upgrade, then Dr. Radcliffe's declaration does not show Asano was either. Teleflex may have made a plausible argument that Asano is inefficient as compared to Engelgau's preferred embodiment, but to judge Asano against Engelgau would be to engage in the very hindsight bias Teleflex rightly urges must be avoided. Accordingly, Teleflex has not shown anything in the prior art that taught away from the use of Asano.

Like the District Court, finally, we conclude Teleflex has shown no secondary factors to dislodge the determination that claim 4 is obvious. Proper application of *Graham* and our other precedents to these facts therefore leads to the conclusion that claim 4 encompassed obvious subject matter. As a result, the claim fails to meet the requirement of § 103.

We need not reach the question whether the failure to disclose Asano during the prosecution of Engelgau voids the presumption of validity given to issued patents, for claim 4 is obvious despite the presumption. We nevertheless think it appropriate to note that the rationale underlying the presumption—that the PTO, in its expertise, has approved the claim—seems much diminished here.

IV

[8] A separate ground the Court of Appeals gave for reversing the order for summary judgment was the existence of a dispute over an issue of material fact. We disagree with the Court of Appeals on this point as well. To the extent the court understood the *Graham* approach to exclude the possibility of summary judgment when an expert provides a conclusory affidavit addressing the question of obviousness, it misunderstood the role expert testimony plays in the analysis. In considering summary judgment on that question the district court can and should take into account expert testimony, which may resolve or keep open certain questions of fact. That is not the end of the issue, however. The ultimate judgment of obviousness is a legal determination. *Graham*, 383 U.S., at 17. Where, as here, the content of the prior art, the scope of the patent claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate. Nothing in the declarations proffered by Teleflex prevented the District Court from reaching the careful conclusions underlying its order for summary judgment in this case.

* * *

We build and create by bringing to the tangible and palpable reality around us new works based on instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more. And as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts. See U.S. Const., Art. I, § 8, cl. 8. These premises led to the bar on patents claiming obvious subject matter established in *Hotchkiss* and codified in § 103. Application of the bar must not be confined within a test or formulation too constrained to serve its purpose.

KSR provided convincing evidence that mounting a modular sensor on a fixed pivot point of the Asano pedal was a design step well within the grasp of a person of ordinary skill in the relevant art. Its arguments, and the record, demonstrate that claim 4 of the Engelgau patent is obvious. In rejecting the District Court's rulings, the Court of Appeals analyzed the issue in a narrow, rigid manner inconsistent with § 103 and our precedents. The judgment of the Court of Appeals is reversed, and the case remanded for further proceedings consistent with this opinion.

It is so ordered.

Microsoft Corp. v. AT&T Corp.

U.S. Supreme Court
No. 05-1056
Decided April 30, 2007

PATENTS

[1] Infringement — In general (§ 120.01)

International issues — In general (§ 157.01)

Patent on apparatus for digitally encoding and compressing recorded speech is not infringed, under 35 U.S.C. § 271(f), by computers made in another country when loaded with operating system software copied abroad from master disk or electronic transmission sent by defendant from United States, since master disk or electronic transmission defendant sends from United States is never installed on any of foreign-made computers in question, and since defendant therefore does not "suppl[y] . . . from the United States" any "components" of computers in question within meaning of Section 271(f), in that defendant does not export copies of software that are actually installed on computers.

[2] Infringement — Inducement (§ 120.15)

International issues — In general (§ 157.01)

Computer software in abstract form of code or instructions detached from any medium does not qualify as "component" of patented invention for purposes of 35 U.S.C. § 271(f)(1), which imposes liability for supplying "components" of patented invention from United States "in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combi-

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GB 1375986 A EP 0694308 A1 EP 0474126 A1
EP 0139891 A2 EP 0010437 A2 WO 95/04551 A1
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(54) Abstract Title
Stabilisation of Macrolide Compositions

(57) A pharmaceutical composition for oral or parenteral administration comprising a macrolide, preferably a rapamycin or a macrolide of the FK 506 class, is stabilised by the presence of an a mono-, di- or tricarboxylic acid, preferably malonic acid.

GB 2 327 611 A

Macrolide compositions

This application is derived from GB 9707483.5.

This invention relates to stabilisation of macrolides.

The term "macrolide" as used herein, refers to a macrocyclic lactone, for example a compound having a 12- membered or larger lactone ring. Of particular interest are the "lactam macrolides", i.e., macrocyclic compounds having a lactam (amide) bond in the macrocycle in addition to a lactone (ester) bond, for example the lactam macrolides produced by microorganisms of the genus Streptomyces such as rapamycin, ascomycin, and FK-506, and their numerous derivatives and analogues. Such lactam macrolides have been shown to have interesting pharmaceutical properties, particularly immunosuppressive and anti-inflammatory properties.

Rapamycin is an immunosuppressive lactam macrolide that is produced by Streptomyces hygroscopicus. The structure of rapamycin is given in Kesseler, H., et al.; 1993; Helv. Chim. Acta; 76: 117. See, e.g., McAlpine, J.B., et al., J. Antibiotics (1991) 44: 688; Schreiber, S.L., et al., J. Am. Chem. Soc. (1991) 113: 7433; US Patent No. 3 929 992. Rapamycin is an extremely potent immunosuppressant and has also been shown to have antitumor and antifungal activity. Its utility as a pharmaceutical, however, is restricted by its very low and variable bioavailability as well as its high toxicity. Numerous derivatives of rapamycin are known. Certain 16-O-substituted rapamycins are disclosed in WO 94/02136, the contents of which are incorporated herein by reference. 40-O-substituted rapamycins are described in, e.g., in US 5 258 389 and WO 94/09010 (O-aryl and O-alkyl rapamycins); WO 92/05179 (carboxylic acid esters), US 5 118 677 (amide esters), US 5 118 678 (carbamates), US 5 100 883 (fluorinated esters), US 5 151 413 (acetals), US 5 120 842 (silyl ethers), WO 93/11130 (methylene rapamycin and derivatives), WO 94/02136 (methoxy derivatives), WO 94/02385 and WO 95/14023 (alkenyl derivatives) all of which

are incorporated herein by reference. 32-O-dihydro or substituted rapamycin are described, e.g., in US 5 256 790, incorporated herein by reference.

Rapamycin and its structurally similar analogues and derivatives are termed collectively as "rapamycins".

Ascomycins, of which FK-506 and ascomycin are the best known, comprise another class of lactam macrolides, many of which have potent immunosuppressive and anti-inflammatory activity. FK506 is a lactam macrolide immunosuppressant that is produced by Streptomyces tsukubaensis No 9993. The structure of FK506 is given in the appendix to the Merck Index, 11th ed. (1989) as item A5. Ascomycin is described, e.g., in US patent 3,244,592. Many derivatives of ascomycin and FK-506 have been synthesized, including halogenated derivatives such as 33-epi-chloro-33-desoxy-ascomycin described in EP 427 680. Ascomycin, FK-506 and their structurally similar analogues and derivatives are termed collectively "ascomycins".

The macrolide may, therefore, be rapamycin or an O-substituted derivative in which the hydroxyl group on the cyclohexyl ring of rapamycin is replaced by $-OR_1$ in which R_1 is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin.

A preferred compound is 40-0-(2-hydroxy)ethyl rapamycin as disclosed in WO 94/09010.

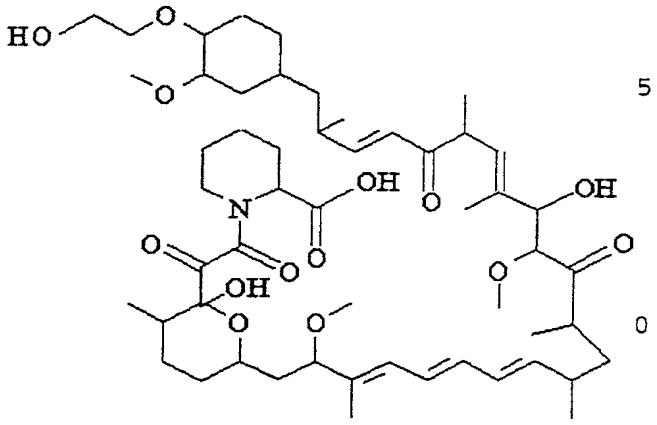
Examples of compounds of the FK 506 class are those mentioned above. They include for example FK 506, ascomycin and other naturally occurring compounds. They include also synthetic analogues.

A preferred compound of the FK 506 class is disclosed in EP 427 680, e.g. Example 66a also known as 33-epi-chloro-33-desoxy-ascomycin. Other preferred compounds are disclosed in EP 465 426, and in EP 569 337, e.g. the compound of Example 71 in EP 569

337.

The present applicants have found that macrolides are unstable upon storage, for example 40-0-(2-hydroxy)ethyl rapamycin, and can undergo a variety of different degradation reactions. Upon storage, for example, of several days, one or more degradation products may be identified, e.g. using HPLC. Although degradation pathways have yet to be identified, the applicants believe that rupture of the macrolide lactone ring may occur.

The present applicants have identified as 40-0-(2-hydroxy)ethyl rapamycin-2,34-secoacid as a main degradation product of 40-0-(2-hydroxy)ethyl rapamycin. 40-0-(2-hydroxy)ethyl rapamycin-2,34-secoacid, referred to hereinafter as secoacid, has the following structure:

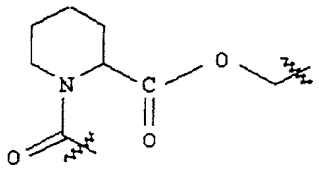


It has now been found that stable compositions containing macrolides may be obtained by formulating the macrolide in an acidic environment. Compositions are understood herein to be stable when the macrolide drug substance remains substantially intact after a period of days or weeks at room temperature (25°C).

In one aspect this invention provides a pharmaceutical composition comprising a macrolide and an acid.

The term macrolide has the meaning as described above.

Preferred macrolides have at least one moiety as follows



Examples are those mentioned above and are preferably rapamycin or 40-0-(2-hydroxy)ethyl rapamycin.

The acid may be lipid soluble and/or ethanol soluble. The acid may be for example a fatty acid, e.g. oleic acid. The acid may be a carboxylic acid, for example a mono-, di- or tri-carboxylic acid, and preferably a mono- or dicarboxylic acid. The acid may comprise one or more hydrophilic groups, e.g. hydroxy groups, and preferably one or two hydrophilic groups. Suitable acids for use in this invention include malonic acid, fumaric acid, maleic acid, D-malic acid, L-malic acid, citric acid, ascorbic acid, succinic acid, oxalic acid, benzoic acid or lactic acid or an acid with a similar pKa, e.g. 2-7. Preferred acids include malonic acid, oxalic acid, citric acid and lactic acid. Malonic acid is more preferred.

The preferred amount of acid may be determined by routine experimentation. The ratio by weight of macrolide to acid in the compositions of this invention may be up to 20:1, for example from 1:5 to 5:1, e.g. 1:1. The acid may be present in an amount of between 0.05% and 5% by weight of the macrolide compositions disclosed in application GB 9707483.5.

The macrolide may be present in an amount of 1 to 15 % by weight of the macrolide compositions disclosed in application GB 9707483.5.

The type of pharmaceutical composition is not critical. It may be solid, but it is preferably liquid. The macrolide may, for example, be formulated into a microemulsion preconcentrate or emulsion preconcentrate as defined in GB 9707483.5, and combined with an amount of acid. The acid-stabilised composition may be administered enterally, e.g orally, e.g. as a capsule or drink solution, or parenterally, e.g. as an infusion concentrate.

In another aspect, this invention provides the use of an acid to stabilise a macrolide in a pharmaceutical composition.

In another aspect, this invention provides a method of stabilising a macrolide in a pharmaceutical composition, which method comprises mixing an acid with the macrolide.

This invention thus allows preparation of stable macrolide compositions. Good drug bioavailability and low variability in inter- and intra-patient dose response may be obtained.

Following is a description by way of example only of macrolide compositions stabilised by an acid.

Example 1

An active agent of the FK 506 class or rapamycin class e.g. 40-0-(2-hydroxy)ethyl rapamycin is made up into a microemulsion preconcentrate having the following composition by weight 2% active compound, 2% malonic acid, lactic acid or famonic acid, 44% Cremophor RH40 26.4% corn-oil mono-, di-, tri-glycerides, 17.6% 1,2 propylene glycol and 10% ethanol.

Stability tests over 3 months showed that a malonic acid composition contained 98% of active agent thereafter and without the malonic acid only 73%.

Examples 2 and 3

Microemulsion preconcentrates are prepared using 40-0-(2-hydroxy)ethyl rapamycin in

Examples 2a and 2b, and rapamycin in Examples 3a and 3b as active agent. In Example 2, the active agent 40-0-(2-hydroxy)ethyl rapamycin is abbreviated to "active agent R".

Intact drug content and main degradation product are determined by HPLC with an analytical error of +/- 2%.

Composition	Example 2a active agent R	Example 2b active agent R malonic acid	Example 3a Rapamycin	Example 3b Rapamycin malonic acid
Cremophor RH 40	44.0 %	43.0 %	41.5 %	40.5 %
Cornoil glyceride	26.3 %	25.7 %	24.8 %	24.2 %
Propylene glycol	17.6 %	17.2 %	16.6 %	16.2 %
Ethanol abs.	10.0 %	10.0 %	15.0 %	15.0 %
DL-α-Tocopherol	0.1 %	0.1 %	0.1 %	0.1 %
active agent R	2.0 %	2.0 %	-	-
Rapamycin	-	-	2.0 %	2.0 %
Malonic acid	-	2.0 %	-	2.0 %
Intact drug content and main degradation product (seco acid) expressed as percentages of amount (HPLC evaluation by external standardization)				
4 weeks at 25°C	86.0% (16.1 %)	99.5 % (0.5 %)	83.5 % (15.4 %)	98.4 % (0.7 %)

Amount of main degradation product is shown in brackets. Main degradation product of rapamycin is referred to as secorapamycin.

The above examples demonstrate that malonic acid exhibits a pronounced stabilizing effect on the degradation of 40-0-(2-hydroxy)ethyl rapamycin and of rapamycin.

Example 4

The composition of Example 2a is mixed with malonic acid at concentrations between 0.05 % and 5% by weight. A highly stabilising effect is observed with malonic acid in the concentration range 0.25 to 0.75% by weight of the composition.

Example 5

A concentrate for infusion is prepared using the following composition:

40-0-(2-hydroxy)ethyl rapamycin	20 mg/ml
Cremophor EL	600mg/ml
citric acid	10mg/ml
ethanol	to 1ml

After 4 weeks storage at 25°C, an active ingredient assay of 99.6% is obtained. This demonstrates that citric acid has a stabilising effect on 40-0-(2-hydroxy)ethyl rapamycin.

In the above Examples 1 to 5 the active agent may replaced by 33-epi-chloro-33-desoxy-ascomycin or by the compound of Example 71 in EP 569 337.

Claims

1. A pharmaceutical composition comprising a macrolide and an acid.

2. A composition as claimed in claim 1 wherein the acid is present in an amount of between 0.05 % and 5% by weight of the composition.

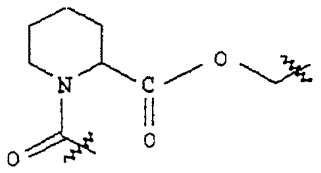
3. A composition as claimed in claim 1 or 2 wherein the ratio by weight of macrolide to acid is up to 20:1, e.g. 1:5 to 5:1.

4. A composition as claimed in any preceding claim wherein the macrolide is an ascomycin or a rapamycin.

5. Use of an acid to stabilise a macrolide against degradation in a pharmaceutical composition.

6. A method of stabilising a macrolide against degradation in a pharmaceutical composition, which method comprises mixing an acid with the macrolide.

7. A method as claimed in claim 6 wherein the macrolide has at least one moiety as follows



8. A method as claimed in claim 6 or 7 wherein the acid is a fatty acid or a mono-, di- or tri-carboxylic acid.

9. A method as claimed in claim 6, 7 or 8 wherein the ratio by weight of macrolide to acid is up to 20:1, e.g. 1:5 to 5:1.

10. A method as claimed in any one of claims 6 to 9 wherein the macrolide is an ascomycin or a rapamycin.

11. A composition as claimed in any one of claims 1 to 4, use or method as claimed in any one of claims 5 to 10 wherein the acid is malonic acid, fumaric acid, maleic acid, D-malic acid, L-malic acid, citric acid, ascorbic acid, succinic acid, oxalic acid, benzoic acid or lactic acid.

12. A composition substantially as herein described with reference to the Examples.

13. Method for stabilising a macrolide against degradation substantially as herein described with reference to the Examples.

The Patent Office

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Application No: GB 9818245.4 **Examiner:** Simon M. Fortt
Claims searched: 1-13 **Date of search:** 20 November 1998

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.P): A5B (BKA)

Int Cl (Ed.6): A61K 31/435, 31/365, 38/13, 47/12.

Other: On-line: CAS-ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB 1 375 986	(GORDON et al.) whole document particularly p 1, ll 12-17, p 2, ll 54-73, examples	1, 5-6, 8
X, E	EP 0 694 308 A1	(SHISEIDO COMPANY) whole document particularly p 2, ll 49-53, p 3, ll 45-54, examples 4 and 7, experi-ment 1.	1-3, 5-6, 8-9
X	EP 0 474 126 A1	(FUJISAWA PHARMACEUTICAL) p 2, ll 5-6, p 3, l 6 - p 4, l 5, p 6, ll 3-5, example 16.	1-10
X	EP 0 139 891 A2	(B.T.B. INDUSTRIA CHIMICA) whole document particularly p 1, ll 1-18, p 2, ll 9-12, p 14, ll 1-26,	1-3, 5-6, 8-9
X	EP 0 010 437 A2	(ELI LILLY COMPANY) whole document	1-3, 5-6, 8-9, 11
X, P	WO 95/04551 A1	(FUJISAWA PHARMACEUTICAL) see equivalent document US 5, 747, 069 col. 1, ll 44-47, 59-67, col. 3, ll 1-19, 33-54, example 2 (4-6 and 10-12).	1-10

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

The Patent Office

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Application No: GB 9818245.4
Claims searched: 1-13

Examiner: Simon M. Fortt
Date of search: 20 November 1998

Category	Identity of document and relevant passage	Relevant to claims
X	WO 90/03793 A1 (MADHOK) whole document	1-3, 5-6, 8-9

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

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(19) **United States**

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Azrolan et al. (43) **Pub. Date: Jan. 31, 2002**

(54) **METHOD OF TREATING CARDIOVASCULAR DISEASE**

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Related U.S. Application Data

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Publication Classification

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(52) **U.S. Cl.** **514/291**

(57) **ABSTRACT**

This invention provides a method of treating or inhibiting cardiovascular, cerebral vascular, or peripheral vascular disease in a mammal in need thereof, which comprises providing said mammal with an effective amount of a rapamycin.

METHOD OF TREATING CARDIOVASCULAR DISEASE

[0001] This application claims the benefit of U.S. Provisional Application No. 60/212,117, filed Jun. 16, 2000.

BACKGROUND OF THE INVENTION

[0002] This invention relates the use of a rapamycin in the treatment and inhibition of cardiovascular disease, cerebral vascular disease, and peripheral vascular disease.

[0003] Coronary artery disease, the primary form of cardiovascular disease (CVD), is the major cause of death in the United States today, responsible for over 550,000 deaths per year. Cerebrovascular disease is the third leading cause of death in the United States. The etiology of both coronary artery and cerebrovascular diseases is attributed to atherosclerosis. Through its clinical manifestations, atherosclerosis is the major cause of the more than one million heart attacks and approximately 400,000 strokes that occur each year. In addition to the high morbidity and mortality associated with atherosclerosis, it has been estimated that atherosclerosis has cost the United States' economy over $80 billion each year in lost wages, lost productivity, and medical care costs [Levy, R., Am. Heart J. 110: 1116 (1985)]. A substantial body of evidence has established a relationship between hypercholesterolemia and premature atherosclerosis; the higher the levels of plasma cholesterol, the greater the risk of subsequent heart attack. [Steinberg, D., JAMA 264: 3047 (1991); Lipid Research Clinics Program, JAMA 251: 351 (1984); Rifkind, B., Am. J. Cardiol. 54: 30C (1984)]. However, recent information demonstrates that the atherosclerotic process is far more complicated than a simple correlation with plasma lipid levels, and that there are both systemic and local factors within the vascular wall that play a major role in the progression of this disease [Sulistiyani, Adelman, S. J., Chandrasekaran, A., Jayo, J. and St. Clair, R. W. Arteriosclerosis and Thrombosis 15: 837, (1995)].

[0004] Atherosclerosis is a complex disease that is associated with a variety of etiologic factors. Studies have shown that, of the major factors involved, diet-induced hyperlipidemia and genetic defects or abnormalities in lipoprotein metabolism have received the most attention. The local disease process of atherosclerosis is characterized by the accumulation of lipids in the walls of blood vessels. Concomitant with lipid accumulation, there is vascular cell damage resulting in dysfunction of the endothelium, smooth muscle proliferation, and matrix deposition. These changes ultimately result in the formation of what is termed "plaque". As these plaques expand and mature, ruptures in their surface can occur, leading to major thrombotic events. This process, which can occur in essentially all of the blood vessels of the body, results in many of the major disease categories of our time, including coronary artery disease, peripheral vascular disease, myocardial infarction and stroke.

[0005] Recently, it has been discovered that cells of the immune system play a major role in all of the processes of atherosclerosis, and thus the process has been described as a chronic inflammatory-fibroproliferative disease of the vascular wall. The attachment of monocytes and T-lymphocytes to the injured endothelium followed by their migration into the intima is one of the first and most crucial steps in lesion development. The co-localization of CD4+ T-cells and macrophages in the lesion, the abundant expression of HLA Class II molecules and the co-stimulatory molecule CD40 and its ligand (CD40L) indicate a contribution of cell-mediated immunity to atherogenesis. A wide variety of studies in animal models suggest that T- and B-cells, and monocytes and macrophages promote lesion progression, and in fact, are in essential for the development of atherosclerotic lesions. Importantly, the local vascular wall immune contribution continues throughout, participating in both plaque expansion as well as rupture. In addition to the local process in the vessel wall, systemic signs of an inflammatory reaction are also associated with lesion development. Thus plasma levels of C-reactive protein and fibrinogen and the white blood cell count are positively correlated to the risk of cardiovascular disease.

[0006] Rapamycin is a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus,* which was found to have antifungal activity, particularly against *Candida albicans,* both in vitro and in vivo [C. Vezina et al., J. Antibiot. 28, 721 (1975); S. N. Sehgal et al., J. Antibiot. 28, 727 (1975); H. A. Baker et al., J. Antibiot. 31, 539 (1978); U.S. Pat. No. 3,929,992; and U.S. Pat. No. 3,993,749]. Additionally, rapamycin alone (U.S. Pat. No. 4,885,171) or in combination with picibanil (U.S. Pat. No. 4,401,653) has been shown to have antitumor activity.

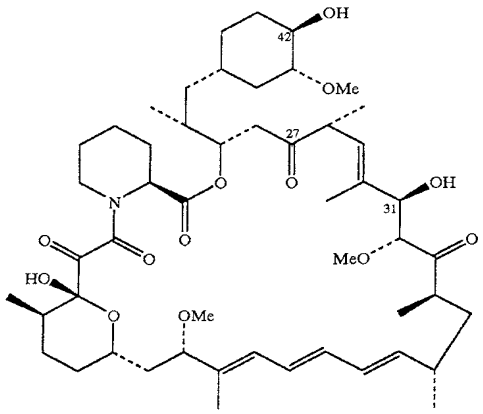
[0007] The immunosuppressive effects of rapamycin have been disclosed in FASEB 3, 3411 (1989). Cyclosporin A and FK-506, other macrocyclic molecules, also have been shown to be effective as immunosuppressive agents, therefore useful in preventing transplant rejection [FASEB 3, 3411 (1989); FASEB 3, 5256 (1989); R. Y. Caine et al., Lancet 1183 (1978); and U.S. Pat. No. 5,100,899]. R. Martel et al. [Can. J. Physiol. Pharmacol. 55, 48 (1977)] disclosed that rapamycin is effective in the experimental allergic encephalomyelitis model, a model for multiple sclerosis; in the adjuvant arthritis model, a model for rheumatoid arthritis; and effectively inhibited the formation of IgE-like antibodies.

[0008] Rapamycin is also useful in preventing or treating systemic lupus erythematosus [U.S. Pat. No. 5,078,999], pulmonary inflammation [U.S. Pat. No. 5,080,899], insulin dependent diabetes mellitus [U.S. Pat. No. 5,321,009], skin disorders, such as psoriasis [U.S. Pat. No. 5,286,730], bowel disorders [U.S. Pat. No. 5,286,731], smooth muscle cell proliferation and intimal thickening following vascular injury [U.S. Pat. Nos. 5,288,711 and 5,516,781], adult T-cell leukemia/lymphoma [European Patent Application 525,960 A1], ocular inflammation [U.S. Pat. No. 5,387,589], malignant carcinomas [U.S. Pat. No. 5,206,018], cardiac inflammatory disease [U.S. Pat. No. 5,496,832], and anemia [U.S. Pat. No. 5,561,138].

DESCRIPTION OF THE INVENTION

[0009] This invention provides a method of treating or inhibiting cardiovascular disease or peripheral vascular disease in a mammal in need thereof, which comprises providing an effective amount of a rapamycin to said mammal. As defined herein, the term "a rapamycin" defines a class of immunosuppressive compounds which contain the basic rapamycin nucleus (shown below). The rapamycins of this invention include compounds which may be chemically or

biologically modified as derivatives of the rapamycin nucleus, while still retaining immunosuppressive properties. Accordingly, the term "a rapamycin" includes esters, ethers, oximes, hydrazones, and hydroxylamines of rapamycin, as well as rapamycins in which functional groups on the rapamycin nucleus have been modified, for example through reduction or oxidation. The term "a rapamycin" also includes pharmaceutically acceptable salts of rapamycins, which are capable of forming such salts, either by virtue of containing an acidic or basic moiety.



RAPAMYCIN

[0010] It is preferred that the esters and ethers of rapamycin are of the hydroxyl groups at the 42- and/or 31-positions of the rapamycin nucleus, esters and ethers of a hydroxyl group at the 27-position (following chemical reduction of the 27-ketone), and that the oximes, hydrazones, and hydroxylamines are of a ketone at the 42-position (following oxidation of the 42-hydroxyl group) and of 27-ketone of the rapamycin nucleus.

[0011] Preferred 42- and/or 31-esters and ethers of rapamycin are disclosed in the following patents, which are all hereby incorporated by reference: alkyl esters (U.S. Pat. No. 4,316,885); aminoalkyl esters (U.S. Pat. No. 4,650,803); fluorinated esters (U.S. Pat. No. 5,100,883); amide esters (U.S. Pat. No. 5,118,677); carbamate esters (U.S. Pat. No. 5,118,678); silyl ethers (U.S. Pat. No. 5,120,842); aminoesters (U.S. Pat. No. 5,130,307); acetals (U.S. Pat. No. 5,51,413); aminodiesters (U.S. Pat. No. 5,162,333); sulfonate and sulfate esters (U.S. Pat. No. 5,177,203); esters (U.S. Pat. No. 5,221,670); alkoxyesters (U.S. Pat. No. 5,233,036); O-aryl, -alkyl, -alkenyl, and -alkynyl ethers (U.S. Pat. No. 5,258,389): carbonate esters (U.S. Pat. No. 5,260,300); arylcarbonyl and alkoxycarbonyl carbamates (U.S. Pat. No. 5,262,423): carbamates (U.S. Pat. No. 5,302, 584); hydroxyesters (U.S. Pat. No. 5,362,718); hindered esters (U.S. Pat. No. 5,385,908); heterocyclic esters (U.S. Pat. No. 5,385,909); gem-disubstituted esters (U.S. Pat. No. 5,385,910); amino alkanoic esters (U.S. Pat. No. 5,389,639); phosphorylcarbamate esters (U.S. Pat. No. 5,391,730); carbamate esters (U.S. Pat. No. 5,411,967); carbamate esters (U.S. Pat. No. 5,434,260); amidino carbamate esters (U.S. Pat. No. 5,463,048); carbamate esters (U.S. Pat. No. 5,480, 988); carbamate esters (U.S. Pat. No. 5,480,989); carbamate esters (U.S. Pat. No. 5,489,680); hindered N-oxide esters (U.S. Pat. No. 5,491,231); biotin esters (U.S. Pat. No. 5,504,091); O-alkyl ethers (U.S. Pat. No. 5,665,772); and PEG esters of rapamycin (U.S. Pat. No. 5,780,462). The preparation of these esters and ethers are disclosed in the patents listed above.

[0012] Preferred 27-esters and ethers of rapamycin are disclosed in U.S. Pat. No. 5,256,790, which is hereby incorporated by reference. The preparation of these esters and ethers are disclosed in the patents listed above.

[0013] Preferred oximes, hydrazones, and hydroxylamines of rapamycin are disclosed in U.S. Pat. Nos. 5,373, 014, 5,378,836, 5,023,264, and 5,563,145, which are hereby incorporated by reference. The preparation of these oximes, hydrazones, and hydroxylamines are disclosed in the above listed patents. The preparation of 42-oxorapamycin is disclosed in U.S. Pat. No. 5,023,263, which is hereby incorporated by reference.

[0014] Particularly preferred rapamycins include rapamycin [U.S. Pat. No. 3,929,992], rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid [U.S. Pat. No. 5,362,718], and 42-O-(2-hydroxy)ethyl rapamycin [U.S. Pat. No. 5,665,772].

[0015] When applicable, pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, napthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable aids when the rapamycin contains a suitable basic moiety. Salts may also be formed from organic and inorganic bases, such as alkali metal salts (for example, sodium, lithium, or potassium) alkaline earth metal salts, ammonium salts, alkylammonium salts containing 1-6 carbon atoms or dialkylammonium salts containing 1-6 carbon atoms in each alkyl group, and trialkylammonium salts containing 1-6 carbon atoms in each alkyl group, when the rapamycin contains a suitable acidic moiety.

[0016] As used in accordance with this invention, the term "providing," with respect to providing a compound or substance covered by this invention, means either directly administering such a compound or substance, or administering a prodrug, derivative, or analog which will form the equivalent amount of the compound or substance within the body.

[0017] The ability of the rapamycins of this invention to treat or inhibit cardiovascular disease or peripheral vascular disease was confirmed in a standard pharmacological test procedure using ApoE knockout (EKO) mice, which are a well accepted animal model of human atherosclerosis. In this test procedure, rapamycin was used a representative example of a rapamycin of this invention. The procedure used, and results obtained are briefly summarized below.

[0018] Male EKO mice, 4-6 weeks of age, were housed in shoe-box cages and were allowed ad lib food and water. The animals were randomized by weight into 5 groups (N=12-15 mice per group) and were fed Purina Rodent Chow for the first week of the study. Also during this period as well as the remaining 12 weeks of the study, the animals were dosed every 2 days with 0, 1, 2, 4 or 8 mg/kg rapamycin s.c. using

2% Tween-80, 1% carboxymethyl cellulose as the vehicle and Control. The animal diet was switched to a casein-based Western Diet for week 2 to week 13 of the study. At the end of the study period, the animals were euthanized, plasma samples obtained, and the hearts perfused first with saline, then with 10% formalin. Total cholesterol and triglycerides were determined using enzymatic methods with commercially-available kits from Boehringer Mannheim and Wako Biochemicals, respectively, and the Boehringer Mannheim Hitachii 911 Analyzer (Boehringer Mannheim Diagnostic Laboratory Systems, Indianapolis, Ind.). Separation and quantification of plasma lipoproteins were performed using FPLC size fractionation. Briefly, 50-100 ml of serum was filtered and injected into two Superose 6 columns (Amersham Pharmacia Biotech, UK, Ltd) connected in series and eluted at a constant flow rate with 1 mM sodium EDTA and 0.15 M NaCl. Areas of each curve representing VLDL, LDL and HDL were integrated using Millennium software (Waters Technologies Corporation), and each lipoprotein fraction was quantified by multiplying the Total Cholesterol value by the relative percent area of each respective peak. The aortas were carefully isolated and remained in the formalin fixative for 48-72 hours before handling. Atherosclerotic lesions were identified by Oil Red O staining. The vessels were destained, and then imaged using a Nikon SMU800 microscope fitted with a Sony 3CCD video camera system in concert with IMAQ Configuration Utility (National Instrument) as the image capturing software. The lesions were quantified along the aortic arch using a custom threshold utility software package designed by Robert Coil (Coleman Technologies). Automated lesion assessment was performed on the vessels using the threshold function of the program, specifically on the region contained within the aortic arch from the proximal edge of the Right Common Carotid artery to the distal edge of the Left Subclavian artery. Aortic atherosclerosis data were expressed as percent lesion involvement strictly within this defined luminal area. Statistical significance between the Control and treated groups was determined using the Dunnett's Test at 1 % significance level ($p<0.01$).

[0019] The following table summarizes the results obtained in this standard pharmacological test procedure for atherosclerosis.

TABLE 1

The Effect of Rapamycin on Plasma Lipids and Aortic Atherosclerosis in Apo E Deficient mice

Dosage	Triglycerides (mg/dl)	Total Cholesterol (mg/dl)	VLDL-C (mg/dl)	LDL-C (mg/dl)	HDL-C (mg/dl)	Aortic Atherosclerosis (% lesion involvement
Control	104 ± 13	1186 ± 47	807 ± 48	371 ± 13	7 ± 3	39.5 ± 2.6
1 mg/kg+	132 ± 16	1434 ± 35	903 ± 34	508 ± 18*	23 ± 6	21.6 ± 3.1*
2 mg/kg	143 ± 20	1311 ± 80	763 ± 64	517 ± 18*	31 ± 5*	14.9 ± 3.1*
4 mg/kg	136 ± 12	1281 ± 58	749 ± 58	494 ± 10*	38 ± 5*	16.4 ± 2.8*
8 mg/kg	134 ± 9	1167 ± 75	644 ± 58	475 ± 21*	49 ± 3*	12.03 ± 2.3*

Data are mean ± S.E.

+Dosage of rapamycin.

*Significantly different from Control group ($p < 0.01$).

[0020] The results in Table I show that treatment with rapamycin significantly ($p<0.01$) increased levels of HDL-cholesterol and LDL-cholesterol, while not significantly affecting levels of triglycerides, total cholesterol, and VLDL-cholesterol compared with control EKO mice. Table I also shows a marked and dramatic decrease in the level of atherosclerosis in the rapamycin treated mice. While animals of the Control group demonstrated a mean lesion involvement in the aortic arch of 39.6%, atherosclerosis in animals treated with rapamycin was only 21.6% involvement at 1 mg/kg and decreased further to 14%, 16%, and 12% at the 2, 4, and 8 mg/kg dosages, respectively. This represents a dramatic three-fold reduction in aortic atherosclerosis in a well accepted model of human atherosclerosis.

[0021] Based on the results obtained in the standard pharmacological test procedure described above, rapamycins are useful in the treatment or inhibition of cardiovascular disease and peripheral vascular disease. More particularly, the rapamycins of this invention are useful in treating or inhibiting coronary artery disease, cerebrovascular disease, arteriosclerosis, atherosclerosis, nonatheromatous arteriosclerosis, or vascular wall damage from cellular events leading toward immune mediated vascular damage. The rapamycins of this invention are also useful inhibiting stroke or multi-infarct dementia.

[0022] In accordance with this invention, contemplated that a rapamycin may be used as the sole active ingredient to provide the cardiovascular, cerebral, or peripheral vascular benefits covered by this invention, or may be administered in combination with other agents which provide beneficial cardiovascular, cerebral, or peripheral vascular effects. Such agents are generally in the classes of compounds known as ACE inhibitors, such as quinapril, perindopril, ramipril, captopril, trandolapril, fosinopril, lisinopril, moexipril, and enalapril; angiotensin II receptor antagonists, such as candesartan, irbesartan, losartan, valsartan, and telmisartan; fibric acid derivatives, such as clofibrate, and gemfibrozil; HMG Co-A reductase inhibitors, such as cerivastatin, fluvastatin, atorvastatin, lovastatin, pravastatin, simvastatin; beta adrenergic blocking agents, such as sotalol, timolol, esmolol, carteolol, propranolol, betaxolol, penbutolol, nadolol, acebutolol, atenolol, metoprolol, and bisoprolol; calcium channel blockers, such as nifedipine, verapamil, nicardipine, diltiazem, nimodipine, amlodipine, felodipine, nisoldipine, and bepridil; antioxidants; anticoagulants such as, warfarin, dalteparin, heparin, enoxaparin, and danaparoid; and agents useful in hormone replacement

therapy containing estrogens, such as conjugated estrogens, ethinyl estradiol, 17-beta-estradiol, estradiol, and estropipate.

[0023] It is understood that the effective dosage of a rapamycin may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. As used in accordance with invention, satisfactory results may be obtained when the rapamycin is administered in a daily oral dosage of from about 5 μg to 0.75 mg per kilogram of body weight. The projected daily dosages are expected to vary with route of administration.

[0024] When a rapamycin is used as part of a combination regimen, dosages of each of the components of the combination are administered during a desired treatment period. The components of the combination may administered at the same time; either as a unitary dosage form containing both components, or as separate dosage units; the components of the combination can also be administered at different times during during a treatment period, or one may be administered as a pretreatment for the other.

[0025] Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, intranasally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

[0026] Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. It is more preferred that poloxamer 188 is used as the surface modifying agent. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Preferred oral formulations of rapamycins are disclosed in U.S. Pat. Nos. 5,559,121; 5,536,729; 5,989,591; and 5,985,325, which are hereby incorporated by reference.

[0027] In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

[0028] The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparation contain a preservative to prevent the growth of microorganisms.

[0029] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Preferred parenteral formulations for administering a rapamycin are disclosed in U.S. Pat. Nos. 5,530,006; 5,516,770; and 5,616,588, which are hereby incorporated by reference.

[0030] Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

What is claimed is:

1. A method of treating or inhibiting cardiovascular, cerebral vascular, or peripheral vascular disease in a mammal in need thereof, which comprises providing said mammal with an effective amount of a rapamycin.

2. The method according to claim 1, wherein the rapamycin is rapamycin.

3. The method according to claim 1, wherein the rapamycin is a ester, ether, oxime, hydrazone, or hydroxylamine of rapamycin

4. The method according to claim 3, wherein the rapamycin is a 42-ester or 42-ether of rapamycin.

5. The method according to claim 4, wherein the rapamycin is rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid.

6. The method according to claim 4, wherein the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin.

7. The method according to claim 1, wherein the rapamycin is provided in combination with one or more agents selected from the groups consisting of an ACE inhibitor, an

angiotensin II receptor antagonists, a fibric acid derivative, a HMG Co-A reductase inhibitor, a beta adrenergic blocking agent, a calcium channel blocker, an antioxidant; an anticoagulants, or an agent useful in hormone replacement therapy containing an estrogen.

8. A method of treating or inhibiting coronary artery disease, cerebrovascular disease, arteriosclerosis, atherosclerosis, nonatheromatous arteriosclerosis, or vascular wall damage from cellular events leading toward immune mediated vascular damage in a mammal in need thereof, which comprises providing said mammal with an effective amount of a rapamycin.

9. The method according to claim 8, wherein the rapamycin is rapamycin.

10. The method according to claim 8, wherein the rapamycin is a ester, ether, oxime, hydrazone, or hydroxylamine of rapamycin

11. The method according to claim 10, wherein the rapamycin is a 42-ester or 42-ether of rapamycin.

12. The method according to claim 11, wherein the rapamycin is rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid.

13. The method according to claim 11, wherein the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin.

14. The method according to claim 8, wherein the rapamycin is provided in combination with one or more agents selected from the groups consisting of an ACE inhibitor, an angiotensin II receptor antagonists, a fibric acid derivative, a HMG Co-A reductase inhibitor, a beta adrenergic blocking agent, a calcium channel blocker, an antioxidant; an anticoagulants, or an agent useful in hormone replacement therapy containing an estrogen.

15. A method of inhibiting stroke or multiinfarct dementia in a mammal in need thereof, which comprises providing said mammal with an effective amount of a rapamycin.

16. The method according to claim 15, wherein the rapamycin is rapamycin.

17. The method according to claim 15, wherein the rapamycin is a ester, ether, oxime, hydrazone, or hydroxylamine of rapamycin

18. The method according to claim 17, wherein the rapamycin is a 42-ester or 42-ether of rapamycin.

19. The method according to claim 18, wherein the rapamycin is rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid.

20. The method according to claim 18, wherein the rapamycin is 42-O-(2-hydroxy)ethyl rapamycin.

21. The method according to claim 15, wherein the rapamycin is provided in combination with one or more agents selected from the groups consisting of an ACE inhibitor, an angiotensin II receptor antagonists, a fibric acid derivative, a HMG Co-A reductase inhibitor, a beta adrenergic blocking agent, a calcium channel blocker, an antioxidant; an anticoagulants, or an agent useful in hormone replacement therapy containing an estrogen.

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algoscopy (al-gos′ko-pe) [L. *algor* cold + Gr. *skopein* to view] (*obs.*) cryoscopy.

algosis (al-go′sis) the presence of algae or fungi in a part of the body.

algospasm (al′go-spazm) [*algo-* + *spasm*] painful spasm or cramp.

algovascular (al″go-vas′ku-lar) algiovascular.

Ali Abbas (ah′le ab′bas) (10th century A.D.) a celebrated Persian physician who wrote *Al-Maliki* (the "Royal Book"), a comprehensive treatise on medicine.

Ali ben Iza (ah′le ben i′zah) [11th century A.D.] a noted Arabic ophthalmologist, who wrote *Tadhkirat* (or *risala*) *al-kah-halin* (the "Book of Memoranda for Eye-doctors"); known also as *Jesu Haly*.

Alibert's disease, keloid (al-e-berz′) [Jean Louis Marc *Alibert*, French dermatologist, 1768–1837] see *mycosis fungoides*, and under *keloid*.

alible (al′ĭ-b'l) [L. *alibilis*] nutritive; assimilable as a food.

alices (al′ĭ-sēz) [pl.] the red spots that appear before the pustules in smallpox.

alicyclic (al″ĭ-sik′lik) having the properties of both aliphatic and cyclic substances.

Alidase (al′ĭ-dās) trademark for a preparation of hyaluronidase for injection.

alienation (āl″yen-a′shun) [L. *alienatio*] 1. a feeling of disconnection or isolation from the standards and values of society. 2. former term for mental derangement.

alienia (ah″li-e′ne-ah) [*a* neg. + L. *lien* spleen] absence of the spleen.

alienism (āl′yen-izm) [L. *alienus* alien] 1. mental disorder. 2. the practice of forensic psychiatry.

alienist (āl′yen-ist) 1. former term for psychiatrist. 2. a forensic psychiatrist.

aliflurane (al″ĭ-floo′rān) chemical name: 1-chloro-1,2,2,3-tetrafluoro-3-methoxy-cyclopropane; an inhalation anesthetic, $C_4H_3ClF_4O$.

aliform (al′ĭ-form) [L. *ala* wing + *forma* shape] shaped like a wing.

alignment (ah-līn′ment) [Fr. *aligner* to put in a straight line] the act of arranging in a line; the state of being arranged in a line. In dentistry, the bringing of natural teeth into normal articulation, or the arranging of artificial teeth in normal articulation and appearance.

aliment (al′ĕ-ment) [L. *alimentum*] food or nutritive material.

alimentary (al″ĕ-men′tar-e) pertaining to food or nutritive material, or to the organs of digestion.

alimentation (al″ĕ-men-ta′shun) the act of giving or receiving nutriment. **artificial a.,** the giving of food or nourishment to persons who cannot take it in the usual way. **forced a.,** 1. the feeding of a person against his will. 2. the giving of more food to a person than his appetite calls for. **rectal a.,** the administration of concentrated nourishment by instillation into the rectum. **total parenteral a.,** parenteral hyperalimentation.

alimentology (al″ĕ-men-tol′o-je) the science of nutrition.

alimentotherapy (al″ĕ-men″to-ther′ah-pe) [*aliment* + Gr. *therapeia* treatment] dietetic treatment; treatment by systematic feeding.

alinasal (al″e-na′sal) pertaining to the ala nasi.

alinement (ah-līn′ment) alignment.

alinjection (al″in-jek′shun) (*obs.*) repeated injection of alcohol for preserving anatomic specimens.

alipamide (ah-lip′ah-mīd) chemical name: 3-(aminosulfonyl)-4-chloro-2,2-dimethylhydrazine benzoic acid; a diuretic and antihypertensive, $C_9H_{12}ClN_3O_3S$.

aliphatic (al″ĕ-fat′ik) [Gr. *aleiphar, aleiphatos* oil] pertaining to an oil; a term applied to the "open-chain" or fatty series of hydrocarbons.

alipogenic (a-lip″o-jen′ik) not lipogenic; not forming fat.

alipoidic (a″lip-oi′dik) free from lipoids.

alipotropic (ah″lip-o-trop′ik) having no influence on the metabolism of fat.

aliquot (al′ĕ-kwot) the part of a number which will divide it without a remainder; e.g., 2 is an aliquot of 6. By extension, any portion that bears a known quantitative relationship to a whole or to other portions of the same whole, as an aliquot portion of a solution; a sample of a whole taken to determine the quantitative composition of the whole.

alismin (ah-lis′min) an extractive from *Alisma plantago*, or water plantain.

alisphenoid (al-e-sfe′noid) [*ala* + *sphenoid*] 1. pertaining to the greater wing of the sphenoid. 2. a cartilage of the fetal chondrocranium on either side of the basisphenoid; later in development it forms the greater part of the greater wing of the sphenoid.

alizarin (ah-liz′ah-rin) [Arabic *ala sara* extract] a red crystalline dye, 1,2-dihydroxyanthraquinone, $C_6H_4(CO)_2C_6H_2(OH)_2$ prepared synthetically or obtained from madder; its compounds are used as indicators. **a. monosulfonate,** a. red; see under *red*. **a. No. 6,** purpurin (def. 2). **a. red,** see under *red*. **a. yellow, a. yellow g.,** see under *yellow*.

alizarinopurpurin (al″ĭ-zar″ĭ-no-pur′pu-rin) purpurin (def. 2).

alkalemia (al″kah-le′me-ah) [*alkali* + Gr. *haima* blood + *-ia*] increased pH or decreased hydrogen ion concentration of the blood.

alkalescence (al″kah-les′ens) slight or incipient alkalinity.

alkalescent (al″kah-les′ent) having a tendency to alkalinity.

alkali (al′kah-li) [Arabic *al-qalīy* potash] any of a class of compounds which form soluble soaps with fatty acids, turn red litmus blue, and form soluble carbonates. Essentially the hydroxides of cesium, lithium, potassium, rubidium, and sodium, they include also the carbonates of these metals and of ammonia. **caustic a.,** any solid hydroxide of a fixed alkali. **fixed a.,** any of the alkalis except ammonium. **volatile a.,** ammonia, NH_3; also ammonium hydroxide.

alkalify (al-kal′e-fi) to make alkaline.

Alkaligenes (al″kah-lij′e-nēz) *Alcaligenes*.

alkaligenous (al″kah-lij′ĕ-nus) yielding an alkali.

alkalimeter (al″kah-lim′ĕ-ter) [*alkali* + *meter*] an instrument for measuring the alkali contained in any mixture.

alkalimetry (al″kah-lim′ĕ-tre) the measurement of the alkalis present in any substance. **Engel's a.,** a method of determining the alkalinity of the blood by titrating a diluted specimen with normal tartaric acid solution until it reddens litmus paper; the amount of tartaric solution necessary to produce the result indicates the degree of alkalinity of the blood.

alkaline (al′kah-līn) [L. *alkalinus*] having the reactions of an alkali.

alkalinity (al″kah-lin′ĭ-te) the fact or quality of being alkaline.

alkalinization (al″kah-lin″ĭ-za′shun) alkalization.

alkalinize (al′kah-lin-iz″) alkalize.

alkalinuria (al″kah-lin-u′re-ah) [*alkaline* + *urine*] an alkaline condition of the urine.

alkalitherapy (al″kah-li-ther′ah-pe) treatment by alkalis; the administration of large amounts of alkali in the treatment of peptic ulcer and hyperchlorhydria.

alkalization (al″kah-li-za′shun) the act of making alkaline.

alkalize (al′kah-līz) to render alkaline.

alkalizer (al″kah-līz′er) an agent that neutralizes acids or causes alkalinization.

alkalogenic (al″kah-lo-jen′ik) producing alkalinity.

alkaloid (al′kah-loid″) [*alkali* + Gr. *eidos* form] one of a large group of nitrogenous basic substances found in plants. They are usually very bitter and many are pharmacologically active. Examples are atropine, caffeine, coniine, morphine, nicotine, quinine, strychnine. The term is also applied to synthetic substances (*artificial a's*) which have structures similar to plant alkaloids, such as procaine. **animal a.,** 1. a ptomaine. 2. a leukomaine. **artificial a.,** an alkaloid that is made by synthetic chemical processes.

alkalometry (al″kah-lom′ĕ-tre) [*alkaloid* + Gr. *metron* measure] the dosimetric administration of alkaloids.

alkalosis (al″kah-lo′sis) a pathologic condition resulting from accumulation of base, or from loss of acid without comparable loss of base in the body fluids, and characterized by decrease in hydrogen ion concentration (increase in pH). Cf. *acidosis*. **altitude a.,** increased alkalinity in blood and tissues due to exposure to high altitudes. **compensated a.,** a condition in which compensatory mechanisms have returned the pH toward normal; see *metabolic a., conpensated*, and *respiratory a., compensated*. **hypokalemic a.,** a variety of metabolic alkalosis associated with a low serum potassium level; retention of alkali or loss of acid occurs in the extracellular (but not intracellular) fluid compartment, although the pH of the intracellular fluid may be below normal. It may be caused by hypertrophy and hypoplasia of the juxtaglomerular cells, as in Bartter's syndrome. **metabolic a.,** a disturbance in which the acid-base status of the body shifts toward the alkaline side because of retention of base or loss of noncarbonic, or fixed (nonvolatile), acids. **metabolic a., compensated,** a state of alkalosis in which the pH of the blood has been returned toward normal by respiratory compensation. **respiratory a.,** a state due to excess loss of carbon dioxide from the body. **respiratory a., compensated,** a respiratory alkalosis in which the pH of the blood has been returned toward normal through retention of acid or excretion of base by renal mechanisms.

alkalotherapy (al″kah-lo-ther′ah-pe) alkalitherapy.

alkalotic (al″kah-lot′ik) pertaining to or characterized by alkalosis.

alkaluria (al″kah-lu′re-ah) the presence of an alkali in the urine.

alkamine (al′kah-min) an alcohol which contains an amine group.

alkane (al′kān) a saturated hydrocarbon of the methane series,

in the treatment of diarrhea, administered orally. Formerly called *camphorated opium tincture.*

paregorism (par′ĕ-gor″izm) addiction to paregoric.

pareidolia (par″ī-do′le-ah) [*para-* + Gr. *eidōlon* phantom + *-ia*] an illusion in which visual images are given a fantastic interpretation.

parelectronomic (par″e-lek″tro-nom′ik) giving no response to electromotive stimuli.

parelectronomy (par″e-lek-tron′o-me) [*para-* + *electric* + Gr. *nomos* law] a condition in which there is a decrease in strength of an electric current passed through a muscle.

pareleidin (par″el-e′ī-din) the keratin of epidermal cells derived from eleidin of the stratum lucidum.

parencephalia (par″en-sĕ-fa′le-ah) [*para-* + Gr. *enkephalos* brain + *-ia*] congenital defect of the brain.

parencephalocele (par″en-sef′ah-lo-sēl) [*parencephalon* + Gr. *kēlē* hernia] hernial protrusion of the cerebellum.

parencephalon (par″en-sef′ah-lon) [*para-* + Gr. *enkephalos* brain] the cerebellum.

parencephalous (par″en-sef′ah-lus) [*para-* + Gr. *enkephalos* brain] having a congenital deformity of the brain.

parenchyma (pah-reng′kĭ-mah) [Gr. "anything poured in beside"] the essential elements of an organ; used in anatomical nomenclature as a general term to designate the functional elements of an organ, as distinguished from its framework, or stroma. **p. of lens,** substantia lentis. **p. tes′tis** [NA], **p. of testis,** the seminiferous tubules, which are located within the lobules of the testis.

parenchymal (pah-reng′kĭ-mal) pertaining to or of the nature of parenchyma.

parenchymatitis (par″eng-kim″ah-ti′tis) inflammation of a parenchyma.

parenchymatous (par″eng-kim′ah-tus) pertaining to or of the nature of parenchyma.

parenchymula (par″eng-kim′u-lah) the embryonic stage next succeeding that called the closed blastula.

Parendomyces (par″en-do-mi′sēz) a former genus of yeastlike fungi, species of which have now been included in the genus *Candida.*

Parenogen (pah-ren′o-jen) trademark for a preparation of fibrinogen (def. 2).

parental (pah-ren′tal) of, pertaining to, or derived from the parents.

parenteral (pah-ren′ter-al) [*para-* + Gr. *enteron* intestine] not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc.

parepicoele (par-ep′ī-sēl) (*obs.*) either of the lateral recesses of the fourth ventricle of the brain.

parepididymis (par″ep-ĭ-did′ĭ-mis) paradidymis.

parepigastric (par″ep-ĭ-gas′trik) near the epigastrium.

parergasia (par″er-ga′ze-ah) [*para-* + Gr. *ergasia* work] 1. Kraepelin's term for perverted functioning, such as closing the eyes instead of putting out the tongue. 2. Meyer's term for personality twist reactions such as schizophrenia.

parergastic (par″er-gas′tik) [*para-* + Gr. *ergon* work] Meyer's term for psychic disorders marked by twist reactions, i.e., incongruities, oddities, mannerisms, or fantastic or passivity projections (schizophrenia and paranoia).

paresis (pah-re′sis, par′ĕ-sis) [Gr. "relaxation"] slight or incomplete paralysis; often used alone to mean general paresis (dementia paralytica). **galloping p.,** an acutely and rapidly progressing paresis. **general p.,** dementia paralytica. **juvenile p.,** a form of general paresis occurring in children as a result of congenital syphilis. **stationary p.,** paresis which has become arrested.

Parest (par′est) trademark for a preparation of methaqualone hydrochloride.

paresthesia (par″es-the′ze-ah) [*para-* + Gr. *aisthēsis* perception] morbid or perverted sensation; an abnormal sensation, as burning, prickling, formication, etc. **Berger's p.,** paresthesia in young persons of one or both lower limbs, accompanied by weakness, but without objective symptoms. **Bernhardt's p.,** meralgia paresthetica. **visceral p.,** an abnormal sensation referred to some viscus; not a mere excess or defect of a normal visceral sensation.

paresthetic (par″es-thet′ik) pertaining to or marked by paresthesia.

paretic (pah-ret′ik) pertaining to or affected with paresis.

parfocal (par-fo′kal) [L. *par* equal + *focus* hearth] retaining correct focus on changing powers in microscopy.

pargyline hydrochloride (par′gĭ-lēn) [USP] chemical name: *N*-methyl-*N*-2-propynylbenzylamine hydrochloride. An antihypertensive, $C_{11}H_{13}N \cdot HCl$, occurring as a white or practically white crystalline powder; administered orally.

Parham band (pahr′am) [F. W. *Parham,* New Orleans surgeon, 1885–1927] see under *band.*

parhedonia (par″he-do′ne-ah) Freud's name for the abnormalities of sexuality, such as the obsessive desire to see, to exhibit, or to touch the sexual organs of oneself or another.

parhormone (par-hor′mōn) any metabolic substance of the body which influences the functions of other organs or tissues. For example, carbon dioxide.

parica (par″ĭ-kah′) a narcotic snuff prepared from the leguminous seeds of *Piptadenia* (*Anadenanthera*) species, a tree of Brazil. The seeds contain dimethyltryptamine and related psychotomimetic indole alkaloids. Called also *cohoba.*

paricine (pah-ris′in) a quinoline alkaloid, $C_{18}H_{18}ON_2$, from the bark of *Cinchona succirubra* Parvon. (Rubiaceae), redbark cinchona.

paries (pa′re-ez), pl. *pari′etes* [L.] a wall; [NA] a general term for the wall of an organ or body cavity. **p. ante′rior vagi′nae** [NA], the wall of the vagina that is intimately associated with the posterior wall of the bladder and urethra. **p. ante′rior ventric′uli** [NA], the wall of the stomach that is directed toward the ventral surface of the body. **p. carot′icus ca′vi tym′pani** [NA], the anterior wall of the tympanic cavity, related to the carotid canal in which is lodged the internal carotid artery. **p. exter′nus duc′tus cochlea′ris** [NA], the external wall of the cochlear duct, adjacent to the outer wall of the cochlea. **p. infe′rior or′bitae** [NA], the inferior wall of the orbit, formed by the orbital surfaces of the maxilla and the zygomatic and palatine bones; called also *floor of orbit.* **p. jugula′ris ca′vi tym′pani** [NA], the floor of the tympanic cavity, which is in intimate relation with the jugular fossa, which lodges the bulb of the internal jugular vein. **p. labyrin′thicus ca′vi tym′pani** [NA], the medial wall of the tympanic cavity. **p. latera′lis or′bitae** [NA], the lateral wall of the orbit, formed by the orbital surfaces of the great wing of the sphenoid bone, the zygomatic bone, and the zygomatic process of the frontal bone. **p. mastoi′deus ca′vi tym′pani** [NA], the posterior wall of the tympanic cavity, related to the mastoid portion of the temporal bone. **p. media′lis or′bitae** [NA], the medial wall of the orbit, formed by parts of the maxillary, lacrimal, ethmoid, and sphenoid bones. **p. membrana′ceus bron′chi** [NA], that part of the wall of the smaller bronchi where the cartilage is deficient. **p. membrana′ceus ca′vi tym′pani** [NA], the outer, or lateral, wall of the tympanic cavity, formed mainly by the tympanic membrane. **p. membrana′ceus tra′cheae** [NA], the posterior part of the wall of the trachea where the cartilaginous rings are deficient. **p. poste′rior vagi′nae** [NA], the wall of the vagina that is intimately associated with the anterior wall of the rectum. **p. poste′rior ventric′uli** [NA], the wall of the stomach that is directed toward the back of the body. **p. supe′rior or′bitae** [NA], the superior wall of the orbit, formed chiefly by the orbital plate of the frontal bone and by the orbital surface of the lesser wing of the sphenoid bone; called also *roof of orbit.* **p. tegmenta′lis ca′vi tym′pani** [NA], the roof of the tympanic cavity, related to part of the petrous portion of the temporal bone. **p. tympan′icus duc′tus cochlea′ris** [NA], tympanic wall of cochlear duct: the wall of the cochlear duct that separates it from the scala tympani, composed of the osseous spiral laminae and the basilar membrane. **p. vestibula′ris duc′tus cochlea′ris** [NA], vestibular wall of cochlear duct: the thin anterior wall of the cochlear duct, which separates it from the scala vestibuli; called also *membrana spiralis ductus cochlearis* [NA alternative] or *spiral membrane of cochlear duct.*

parietal (pah-ri′ĕ-tal) [L. *parietalis*] 1. of or pertaining to the walls of a cavity. 2. pertaining to or located near the parietal bone, as the parietal lobe.

parietes (pah-ri′ĕ-tēz) [L.] plural of *paries.*

parietitis (pah-ri″ĕ-ti′tis) inflammation of the wall of an organ.

parietofrontal (pah-ri″ĕ-to-fron′tal) pertaining to the parietal and frontal bones, gyri, or fissures.

parietography (pah-ri″ĕ-tog′rah-fe) roentgenographic visualization of the walls of an organ. **gastric p.,** roentgenographic visualization of the stomach wall by special technique, as a means of detecting early gastric neoplasm.

parieto-occipital (pah-ri″ĕ-to-ok-sip′ĭ-tal) pertaining to the parietal and occipital bones or lobes.

parietosphenoid (pah-ri″ĕ-to-sfe′noid) pertaining to the parietal and sphenoid bones.

parietosplanchnic (pah-ri″ĕ-to-splank′nik) parietovisceral.

parietosquamosal (pah-ri″ĕ-to-skwah-mo′sal) pertaining to the parietal bone and the squamous portion of the temporal bone.

parietotemporal (pah-ri″ĕ-to-tem′po-ral) pertaining to the parietal and temporal bones or lobes.

parietovisceral (pah-ri″ĕ-to-vis′er-al) both parietal and visceral; pertaining to the walls of a cavity and the viscera within it.

Parinaud's oculoglandular syndrome (conjunctivitis), ophthalmoplegia (pah-rĭ-nōz′) [Henri *Parinaud,* French ophthalmologist, 1844–1905] see under *ophthalmoplegia* and *syndrome.*

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Lehman et al. (6) confirmed the observations and reported that 0.5% was the lowest effective dose. Grice et al. (40) reported that at dose levels of 0.5 and 1% for 1.5 years, NDGA had a strong toxic effect in the rat and induced extensive cystic reticuloendotheliosis of the paracecal lymph nodes, an increase in kidney weight, and loss of tubular function, with distended tubular cells indicating impaired kidney function. NDGA did not affect absolute kidney weights but significantly influenced the kidney-to-body weight ratio (Table 5.5). Rats fed 2% NDGA for shorter periods showed similar pathological changes. The orthoquinone may induce loss of tubular function in the kidneys by affecting the permeability of the lysosomal membranes or by inhibiting the lysosomal enzymes (46).

5.2.2 "Hindered" Phenols

Butylated Hydroxyanisole

Butylated hydroxyanisole (BHA; *tert*-butyl-4-hydroxyanisole) is perhaps the most extensively used antioxidant in the food industry. BHA is used in fats and oils, fat-containing foods, confectioneries, essential oils, food-coating materials, and waxes. BHA is a mixture of two isomers, 2-*tert*-butyl-4-hydroxyanisole (2-BHA) and 3-*tert*-butyl-4-hydroxyanisole (3-BHA), with the commercial compound con-

Table 5.5 Average Terminal Body Weight and Absolute and Relative Kidney Weights of Rats Fed Nordihydroguaiaretic Acid at 0–1% of the Diet for 74 Weeks[a]

			Kidney weight	
Dietary level	Number of rats	Terminal body weight (g)	Absolute (g)	Relative (g/100 g bw)
Males				
0	8	395	2.82	0.71
0.5	8	335**	2.75	0.82**
1.0	7	322**	2.65	0.82**
Females				
0	6	270	2.31	0.86
0.5	9	238**	2.26	0.95*
1.0	9	230**	2.36	1.03*

[a]Values marked with asterisks differ significantly from those of controls: $*P = 0.07$; $**P < 0.01$.
Source: Ref. 40.

taining 90% of the 3-isomer (47). In a recent reevaluation, JECFA allocated an ADI of 0–0.5 mg/kg bw (48).

TOXICOLOGICAL STUDIES

Absorption, Metabolism, and Excretion. The absorption and metabolism of BHA has been studied in rats, rabbits, dogs, monkeys, and humans. BHA was rapidly absorbed from the gastrointestinal tract in rats (49), rabbits (50), dogs, and humans (51), rapidly metabolized, and completely excreted. No evidence of tissue accumulation of BHA was observed in rats or dogs (49,52,53). The major metabolites of BHA were the glucuronides, ether sulfates, and free phenols (Fig. 5.5). The metabolites were excreted in the urine, and unchanged BHA was eliminated in the feces. The proportions of the different metabolites varied in different species and also for different dosage levels. In rabbits dosed orally with 1 g of BHA, 46% of glucuronides, 9% ether sulfates, and 6% free phenols were observed in the urine (50). In rats at lower doses, the metabolism was similar to that of rabbits. Urinary excretion was 86% by 24 h and 91% in 4 days (54). In dogs, nearly 60% of a 350 mg/kg dose was excreted unchanged in the feces. The remaining was excreted as ether sulfate, *tert*-butyl hydroquinone (TBHQ), an unidentified phenol, and some glucuronides. In humans, 22–72% of an oral dose

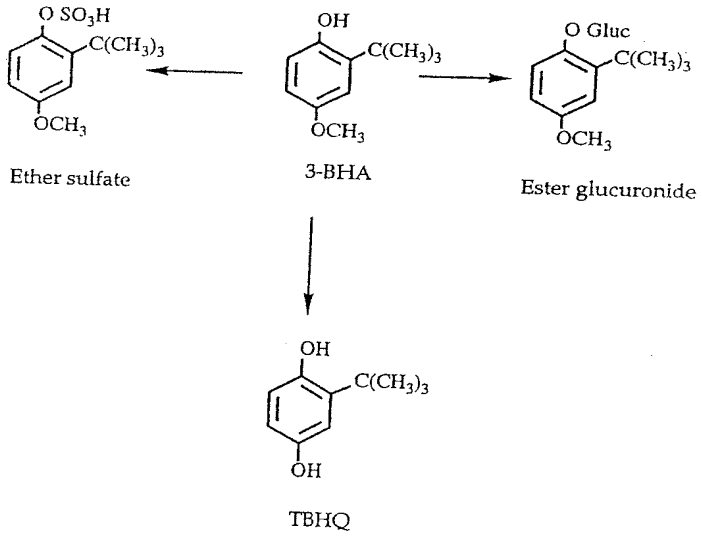

Fig. 5.5 Major metabolites of butylated hydroxyanisole.

of BHA at levels of 0.5–0.7 mg/kg bw was recovered as glucuronides in 24 h, and less than 1% free BHA and very little ether sulfates were observed (51). El-Rashidy and Niazi (55) reported substantial quantities of TBHQ glucuronide or sulfate as a metabolite of the 3-isomer. Later studies confirmed the formation of TBHQ in rats (56,57). Tissue retention of BHA was greater in humans than in rats (58). Much lower doses of BHA were required to produce a given plasma level in humans than in rats (56).

Acute Toxicity. The acute oral LD_{50} was 2200–5000 mg/kb bw in rats and 2000 mg/kg bw in mice (3,6).

Short-Term Studies. Short-term studies have been conducted in a number of species including rats, rabbits, and dogs. Rats administered 500–600 mg/kg bw for a period of 10 weeks showed decreased growth rate and reduced activity of the enzymes catalase, peroxidase, and cholinesterase (59). In rabbits, large doses of BHA (1 g/day) administered by stomach tube for 5–6 days caused a 10-fold increase in sodium excretion and a 20% increase in potassium excretion in the urine (60). No adverse effects were observed in dogs fed 0.3, 30, or 100 mg/kg bw BHA for 1 year (52).

In high doses (500 mg/kg bw per day), BHA induced an increase in the relative liver weight in rats and mice. In rats, the changes follow a complex course that depends on the mode of administration. When rats were given BHA by stomach tube, the relative liver weight increase followed a bimodal time course, with maxima on days 2 and 10 and a highly significant increase on day 7. On dietary administration, liver enlargement was not apparent until day 5, and a single maximum was observed by day 11 (61,62). A preliminary ultrastructural study by Allen and Engblom (63) did not reveal any nucleolar abnormalities in the liver. BHA has been reported to induce a number of hepatic enzymes in rats and mice such as epoxide hydrolase, glutathione-*S*-transferase, glucose-6-phosphate dehydrogenase, and biphenyl-4-hydroxylase (Table 5.6) (61,62,64–66). In dogs, BHA at levels of 1 and 1.3% induced liver enlargement, proliferation of the smooth endoplasmic reticulum, the formation of hepatic myelinoid bodies, and an increase in hepatic enzyme activity (67). Given in doses of 500 mg/kg bw to young rhesus monkeys for 28 days, BHA induced liver hypertrophy and the proliferation of the smooth endoplasmic reticulum. Some differences were observed between monkeys and rats. In monkeys, the activity of microsomal glucose-6-phosphatase was decreased and the nitroanisole demethylase activity was increased, whereas in rats no changes were observed at similar dose levels (63,65).

Long-Term and Carcinogenicity Studies. In earlier long-term studies, BHA was found to be without any toxic effects in rats after 22 months (59,68,69) and in dogs after 15 months (53). However, in later studies, Ito et al. (70–72) reported that in F344 rats, administration of BHA at a 2% level resulted in a high incidence of

Table 5.6 Effects of Butylated Hydroxyanisole Treatment on Hepatic Microsomal and Cytoplasmic Enzyme Activities of Mice[a]

Enzymes	Control group	BHA-treated group
Number of animals	30	12
Microsomal enzymes		
NADPH-cytochrome c reductase (μmol cytochrome c reduced min^{-1} mg^{-1})	0.712 ± 0.028	1.31 ± 0.07
NADH-cytochrome c reductase (μmol cytochrome c reduced min^{-1} mg^{-1})	4.03 ± 0.24	8.22 ± 0.35
Cytochrome P-450 (nmol/mg)	1.53 ± 0.14	1.12 ± 0.10
Cytochrome b_5 (nmol/mg)	0.656 ± 0.061	1.51 ± 0.07
Glucose-6-phosphatase (μmol P_i min^{-1} mg^{-1})	0.509 ± 0.029	0.413 ± 0.066
Aminopyrine demethylase (nmol formaldehyde min^{-1} mg^{-1})	18.7 ± 1.46	13.9 ± 0.84
Aniline hydroxylase (nmol *p*-aminophenol min^{-1} mg^{-1})	2.25 ± 0.16	6.08 ± 0.59
Benzo[a]pyrene hydroxylase (nmol 3-hydroxybenzo[a]pyrene min^{-1} mg^{-1})	2.07 ± 0.16	1.46 ± 0.19
UDP-glucuronyltransferase (nmol UDP-*p*-aminophenol min^{-1} mg^{-1})	25.2 ± 3.15	117.3 ± 8.3
Cytoplasmic enzymes		
Glucose-6-phosphate dehydrogenase (nmol NADPH min^{-1} mg^{-1}	23.3 ± 5.1	88.2 ± 5
UDP-glucose dehydrogenase (nmol NADH min^{-1} mg^{-1})	9.79 ± 1.24	59.8 ± 10.4

[a]BHA was fed at 0.75% (w/w) in the diet for 10 days.
Source: Ref. 64.

papilloma in almost 100% of the treated animals and squamous cell carcinoma of the forestomach in about 30% of the treated animals (Table 5.7). At lower dose levels of 0.5%, no neoplastic lesions were observed, but forestomach hyperplasia was observed. Most of the changes were close to the limiting ridge between the forestomach and the glandular stomach. Ito et al. (72) observed that in addition to 3-BHA, two metabolites *p-tert*-butylphenol and 2-*tert*-butyl-4-methylphenol, also induced papillomas in the forestomach. Verhagen et al. (73) observed that in rats not only the forestomach but also the glandular stomach, small intestine, colorectal tissues, and possibly esophageal tissues were susceptible to the proliferative effects

t on Hepatic Micro-

BHA-treated group
12
1.31 ± 0.07
8.22 ± 0.35
1.12 ± 0.10
1.51 ± 0.07
0.413 ± 0.066
13.9 ± 0.84
6.08 ± 0.59
1.46 ± 0.19
117.3 ± 8.3
88.2 ± 5
59.8 ± 10.4

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Table 5.7 Proliferative and Neoplastic Lesions of the Forestomach Epithelium in F344 Rats Given Diet Containing Butylated Hydroxyanisole

BHA in diet (%)	Effective no. of rats[a]	No. of rats with changes in forestomach[b] (%)		
		Hyperplasia	Papilloma	Squamous-cell carcinoma
0	50	0 (0)	0 (0)	0 (0)
0.125	50	1 (2)	0 (0)	0 (0)
0.25	50	7 (14) *	0 (0)	0 (0)
0.5	50	16 (32) **	0 (0)	0 (0)
1	50	44 (88) **	10 (20)*	0 (0)
2	50	50 (100)**	50 (100)**	11 (22)**

[a]Number surviving at least to week 50.
[b]Asterisked values differ significantly from the control value: $*P < 0.01$; $**P < 0.001$.
Source: Ref. 72.

of BHA. Hamsters were found to be more susceptible to BHA than rats (74). In hamsters fed 1 or 2% BHA for 24 and 104 weeks, forestomach papillomas were observed in almost all treated animals and carcinomas in 7–10% in the 104-week group. A lower incidence of lesions was observed in mice fed 0.5 and 1% BHA (75).

In order to determine which isomer of BHA was carcinogenic or whether the isomers had a synergistic action, feeding studies were conducted with the pure isomers and crude BHA in hamsters for 1–4 weeks. Severe adverse effects were observed with crude BHA and the 3-isomer. The 2-isomer had no effect (76). In rats given 1 g/kg bw of the two isomers, 2-BHA was also active in the induction of forestomach papillomas (77). The forestomach hyperplasia was found to be reversible, but the time taken for recovery depended on the duration and level of treatment. In rats fed 0.1–2% BHA for 13 weeks, on cessation of treatment the forestomach reverted to normal after 9 weeks. In rats fed 2% BHA for 1, 2, or 4 weeks followed by a 4-week recovery period, the mild hyperplasia and epithelial changes observed in the 1-week group almost completely disappeared. The more severe changes observed in the 2- and 4-week groups regressed partially during the recovery period (77).

Because of the possible relevance of these observations to humans, studies were conducted in other species including monkeys and pigs, which, like humans, do not have a forestomach. In female cyanomalgus monkeys, BHA (125 or 500 mg/kg bw) given by gavage for 12 weeks failed to induce any histopathological changes

in the stomach and esophagus. However, a 40% increase in the mitotic index was observed at the lower end of the esophagus (Table 5.8) (78). In dogs fed BHA at levels of 0.25, 0.5, 1, and 1.3% for 6 months, no histopathological changes were noticed in the stomach, esophagus, or duodenum. Liver weights were increased without any related histopathological changes (67,79). Administration of BHA at levels of 50, 200, and 400 mg/kg bw per day to pregnant pigs from mating to day 110 of the gestation period resulted in proliferation and parakeratotic changes in the esophageal epithelium in a few pigs in the two groups with the higher dose levels. But papillomas were not observed, and no changes were found in the glandular stomach (80). In Japanese house musk shrews (*Sancus murinus*), which have no forestomach, BHA was fed at levels of 0.5, 1, and 2% for 80 weeks. All the animals in the 2% group died of hemorrhage in the gastrointestinal tract. Adenomatous hyperplasia in the lungs was observed at the 0.5 and 1% levels at a significantly higher rate (81).

The mechanism by which 3-BHA induces carcinomas in the forestomach is not clear. Studies by De Stafney et al. (82) suggest that two factors may be of importance. One of these entails thiol depletion. The second is an attack by the reactive metabolites of 3-BHA or secondary products produced by these metabolites on cellular constituents. Studies by Williams (83) also indicated that BHA has an effect on membrane systems, blocking the exchange between the hepatocytes and the epithelial cells. The data strongly suggest that BHA is an epigenetic carcinogen that produces forestomach neoplasia through a promoting effect.

Butylated hyroxyanisole has a promoting or inhibitory effect on the carcinogenic effects of a number of chemical carcinogens. BHA enhanced forestomach carcinogenesis initiated by either *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine or *N*-methylnitrosourea (MNU) in rats. BHA had a promoting effect on the urinary bladder carcinogenesis initiated by MNU or *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine and thyroid carcinogenesis initiated by MNU in rats. It had an inhibitory effect on the liver carcinogenesis initiated by either diethylnitrosamine or *N*-ethyl-*N*-

Table 5.8 Mitotic Index of the Esophageal Epithelium from Cyanomalgus Monkeys given 0–250 mg BHA/kg per Day by Gavage on 5 days per week for 12 weeks

BHA treatment (mg kg^{-1} day^{-1})	No. of monkeys	No. of cells counted	No. of cells in mitosis	Mitotic cells (% of total)
0 (control)	8	4860 ± 223	43 ± 7	0.87 ± 0.11
125	7	4921 ± 154	38 ± 6	0.77 ± 0.11
250	7	5485 ± 468	91 ± 10	1.66 ± 0.17*

*$P \leq 0.05$.
Source: Ref. 78.

in the mitotic index was
(78). In dogs fed BHA at
ithological changes were
weights were increased
dministration of BHA at
pigs from mating to day
parakeratotic changes in
ips with the higher dose
nges were found in the
(*Sancus murinus*), which
nd 2% for 80 weeks. All
ie gastrointestinal tract.
ie 0.5 and 1% levels at a

in the forestomach is not
two factors may be of
cond is an attack by the
duced by these metabo-
indicated that BHA has
etween the hepatocytes
BHA is an epigenetic
promoting effect.
y effect on the carcino-
enhanced forestomach
nitrosoguanidine or *N*-
g effect on the urinary
4-hydroxybutyl)nitrosa-
had an inhibitory effect
osamine or *N*-ethyl-*N*-

Cyanomalgus
days per week

Mitotic cells (% of total)
0.87 ± 0.11
0.77 ± 0.11
1.66 ± 0.17*

hydroxyethylnitrosamine and on mammary carcinogenesis initiated by 7,12-dimethylbenz[*a*]anthracene (72).

Reproduction. Butylated hydroxyanisole has not been reported to have any adverse effects on reproduction data or in teratogenicity studies in mice, rats, hamsters, rabbits, pigs, and rhesus monkeys (80,84–88). It has been reported to induce some behavioral abnormalities in mice. Weanling mice exposed to BHA via their mothers during pregnancy and lactation (0.5% level) and then directly for up to 3 weeks showed a significant increase in exploratory activity, decreases in sleeping and in self-grooming, slower learning, and a decrease in the orientation reflex (89). In another study, Stokes et al. (90) observed a decrease in serotonin levels and cholinesterase activity and changed noradrenaline levels in the brain of newborn mice exposed to BHA in utero, and it is postulated that these changes may have an effect on the behavioral modifications observed.

Mutagenicity. Butylated hydroxyanisole was not mutagenic in a number of test systems. It was nonmutagenic in five tester strains in the Ames *Salmonella*/microsome test at concentrations of up to 10 mg/mL (83). In the hepatocyte primary culture/DNA repair test, BHA was negative (91). In mammalian cell mutagenesis assay using adult rat liver epithelial cells (92) and in V79 Chinese hamster lung cells (93), BHA was negative. BHA did not induce sister chromatid exchanges in Chinese hamster overy cells (83). In tests for chromosomal aberrations, BHA was negative in Chinese hamster lung cells and in Chinese hamster DON cells (94,95). In vivo, BHA was negative in rat bone marrow cells and in the rat dominant lethal assay (96).

Butylated Hydroxytoluene

Butylated hydroxytoluene (BHT; 2,6-di-*tert*-butyl-*p*-cresol) is one of the antioxidants used extensively in the food industry. It is used in low-fat foods, fish products, packaging materials, paraffin, and mineral oils. BHT is also widely used in combination with other antioxidants such as BHA, propyl gallate, and citric acid for the stabilization of oils and high-fat foods. ADI values for BHT have changed over the years because of its toxicological effects in different species. The latest temporary value allocated by JECFA is 0–0.125 mg/kg bw (1).

TOXICOLOGICAL STUDIES

Absorption, Metabolism, and Excretion. The absorption, metabolism, and excretion of BHT have been studied in rats, rabbits, dogs, monkeys, and humans. In general, the oxidative metabolism of BHT was mediated by the microsomal monooxygenase system. In rats, rabbits, dogs, and monkeys, oxidation of the *p*-methyl group predominated, whereas in humans the *tert*-butyl groups were oxidized. Oxidation of both *p*-methyl and *tert*-butyl groups was observed in mice.

The metabolism of BHT is more complicated and slower than that of BHA. The relatively slow excretion of BHT has been attributed to the enterohepatic circulation (97–99).

In rats given 0.5 and 1% BHT for 5 weeks, the concentration of BHT increased rapidly in liver and body fat. Approximately 30 ppm was observed in the body fat in males and 45 ppm in females and 1–3 ppm in the liver. On cessation of treatment the concentration in the tissue decreased with a half-life of 7–10 days. In rats given single oral doses of ^{14}C-labeled BHT (1–100 mg/rat), nearly 80–90% was recovered in 4 days, with up to 40% in the urine. Approximately 3.8% was retained in the alimentary tract (98,100–103). The major urinary metabolites observed were BHT-acid (3,5-di-*tert*-butyl-4-hydroxybenzoic acid) (both free and as ester glucuronide) and BHT-mercapturic acid (di-*tert*-butylhydroxybenzyl acetyl cysteine) in addition to many other compounds including BHT alcohol (Ionox-100 or 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol), BHT aldehyde (3,5-di-*tert*-butyl-4-hydroxybenzaldehyde), and BHT dimer. Free BHT acid was the major metabolite in feces. About 10% of the dose was excreted unchanged (101,102, 104,105). Tye et al. (102) observed distinct sex differences in the mode of excretion. Female rats excreted about 40–60% of a single oral dose in feces and about 20–40% in the urine. Males excreted about 70–95% in the feces and 5–9% in the urine. Females showed more tissue retention, especially in the gonads. Significant biliary excretion of BHT and metabolites has also been observed. Four major metabolites have been identified: BHT acid, BHT alcohol, BHT aldehyde, and BHT quinone methide (2,6-di-*tert*-butyl-4-methylene-2,5-cyclohexadienone) (Fig. 5.6) (98,100,106).

The half-life of a single oral dose of BHT in mice was found to be 9–11 h in major tissues such as the stomach, intestine, liver, and kidney. The half-life was 5–10 days when daily doses were given for 10 days. The major metabolite in the urine was the glucuronide conjugate of the acid and free acid in the feces. Excretion was mainly in the feces (41–65%) and urine (26–50%). The formation of BHT quinone methide has been observed in vitro in liver microsomes and in vivo in mouse liver (101).

The major metabolites observed in rabbits were BHT alcohol, BHT acid, and BHT dimer. Excretion of all metabolites was essentially complete in 3–4 days (107). Urinary metabolites constituted 37.5% glucuronides, 16.7% etheral sulfates, and 6.8% free phenols. Unchanged BHT was observed only in the feces (108,109). Significant biliary excretion of BHT and metabolites has also been reported (110). In dogs, the metabolism was similar to that of rats, and significant biliary excretion was observed (111). In monkeys, the major metabolite was the ester glucuronide of BHT acid, and the rate of excretion was similar to that of humans (112). Limited studies in humans (single oral doses of approximately 0.5 mg/kg bw) have indicated that the major metabolite is in the form of an ether-insoluble glucuronide identified as 5-carboxy-7-(1-carboxy-1-methyl ethyl)-3,3-dimethyl-2-hydroxy-2,3-dihydro-

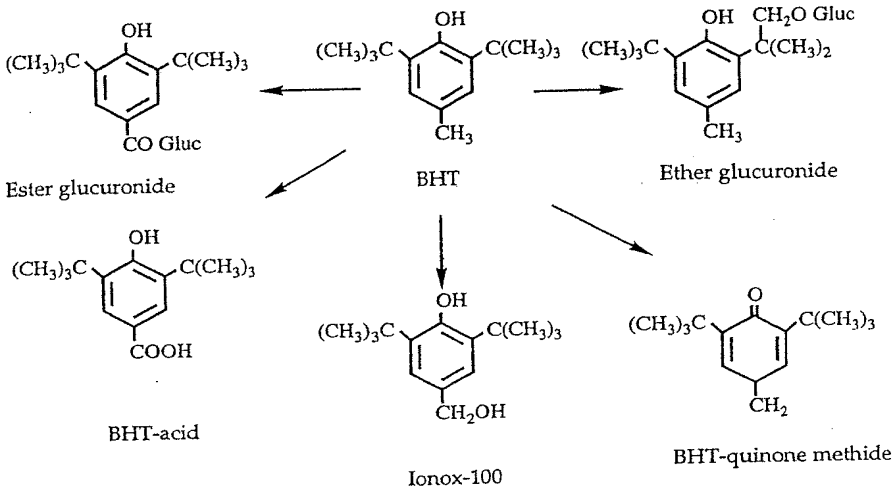

Fig. 5.6 Major metabolites of butylated hydroxytoluene.

benzofuran (99). Daniel et al. (58) studied the excretion of single oral doses of [^{14}C]BHT (40 mg/kg bw) in humans.

Approximately 50% was excreted in the urine in the first 24 h followed by slower excretion for the next 10 days. Tissue retention was found to be greater in humans than in rats. Studies by Wiebe et al. (99) suggest that biliary excretion may be an important route for the elimination of BHT and also that enterohepatic circulation occurs in humans. Verhagen et al. (104) reported differences in the metabolism in rats and humans, especially in terms of plasma kinetics and plasma concentrations, and concluded that the differences were too wide to allow a hazard estimation for BHT consumption by humans on the basis of its metabolism.

Acute Toxicity. The acute oral LD_{50} in mg/kg bw in rats was 1700–1970; in rabbits, 2100–3200; in guinea pigs, 10,700; in cats, 940–2100 (113), and in mice, 2000 (114).

Short-Term Studies. In rats, BHT at the level of 0.3 or 0.5% caused an increase in the level of serum cholesterol and phospholipids within 5 weeks. Brown et al. (69) observed reduced growth rates and increases in liver weight in rats fed BHT at 0.5% in the diet. But at lower dose levels (0.1%) no adverse effects were observed (115). In rabbits at the 2% dose level, BHT caused an acute effect on electrolyte excretion similar to that of BHA, whereas lower levels were without any adverse effect (60). No symptoms of intoxication or histopathological changes were observed in dogs fed 0.17–0.94 mg BHT/kg bw 5 days a week for 12 months (113).

In high doses, BHT had a toxic effect on liver, lung, and kidney and also on the blood coagulation mechanism. Early studies in rats and mice revealed that BHT at 500 mg/kg per day induced liver enlargement in 2 days and stimulated microsomal drug-metabolizing enzyme activity. The effects were found to be reversible (116). Creaven et al. (65) observed that in rats, BHT at levels of 0.01–0.5% for 12 days resulted in increased liver weights and induction of liver microsomal biphenyl-4-hydroxylase activity. At levels of 500 mg/kg bw for 14 days, a reduction in the activity of glucose-6-phosphatase was observed, indicative of early liver damage (115,117). In rats, administration of BHT by gavage at levels of 25, 250, or 500 mg/kg bw for 21 days resulted in a dose-related hepatomegaly, and at the highest dose a progressive periportal hepatocyte necrosis (Table 5.9) (118). The periportal lesions were associated with a proliferation of the bile ducts, persistent fibrosis,

Table 5.9 Summary of Hepatic Histopathology in Rats Treated with Butylated Hydroxytoluene for 7 or 28 Days

Observation	No. of rats with lesion[a] after treatment with BHT in doses (mg kg^{-1} day^{-1}) of:		
	25	250	500
After 7 days			
Periportal region			
Hepatocyte necrosis	0	0	2
Fibrosis	0	0	3
Hepatocyte hypertrophy	0	0	3
Hepatocyte hyperplasia	0	0	4
Glycogen accumulation	0	4	4
After 28 days			
Periportal region			
Hepatocyte necrosis	0	0	6
Fibrosis	0	0	5
Bile-duct cell proliferation	0	0	4
Hepatocyte hypertrophy	0	0	2
Hepatocyte hyperplasia	0	0	3
Pigment-laden macrophages	0	0	3
Glycogen depletion	0	0	7
Glycogen accumulation	0	8	0
Midzonal glycogen accumulation	0	0	5

[a]Out of a total of five per group treated for 7 days and 10 per group treated for 28 days.

Source: Ref. 118.

and infammatory cell reactions. At sublethal dose levels of 1000 and 1250 mg BHT/kg bw for up to 4 days, centrilobular necrosis was observed within 48 h. At a lower dose level (25 mg), no adverse effects were observed. In mice, BHT at levels of 0.75% for 12 months resulted in bile duct hyperplasia (119). The liver hypertrophy was accompanied by a proliferation of the smooth endoplasmic reticulum, an increase in the cytochrome P-450 level, and induction of a number of enzymes, including glutathione-*S*-transferase, glutathione reductase, thymidine kinase, nitroanisole demethylase, epoxide hydrolase, and aminopyrene demethylase. The changes were reversible after the cessation of the treatment (62,118,120, 121). At 500 mg/kg bw for 14 days, BHT caused slight hepatomegaly, moderate proliferation of the smooth endoplasmic reticulum, a reduction in glucose-6-phosphatase, and an increase in nitroanisole demethylase activity in monkeys. At the lower dose of 50 mg/kg bw, no adverse effects were observed (63).

In a more recent study, Takahashi (122) reported that BHT in very high doses (1.35–5% for 30 days) caused a dose-related toxic nephrosis with tubular lesions in mice. The lesions appeared as irregular patches or wedge-shaped proximal tubules, necrosis, and cyst formation. Renal toxicity has also been reported in rats (123,124).

Butylated hydroxytoluene was reported to cause extensive internal and external hemorrhages in rats due to a disruption of the blood coagulation mechanism, resulting in increased mortality (125,126). The minimum effective dose was found to be 7.5 mg/kg bw per day. The disruption observed in the blood coagulation was due to hypoprothrombinemia brought about by inhibition of phylloquinone epoxide reductase activity in the liver by BHT quinone methide, one of the reactive metabolites of BHT (127). Administration of vitamin K prevented the BHT-induced hemorrhage. Takahashi and Hirage (128) suggested that BHT may inhibit absorption of vitamin K in the intestines or uptake by the liver. An increased fecal excretion of vitamin K was observed in rats receiving 0.25% BHT for 2 weeks. BHT was also reported to affect platelet morphology, fatty acid composition of the platelets, and vascular permeability, which may play a role in the hemorrhagic effect (129).

In mice, Takahashi (122) observed that BHT at levels of 0.5, 1, or 2% for 21 days caused massive hemorrhages in the lungs and blood pooling in various organs but only a slight reduction in blood coagulating activity. It was suggested that the hemorrhages might be due to a severe lung injury and not to a coagulation defect as observed in rats. BHT did not cause significant hemorrhaging in guinea pigs at dietary levels of 0–2%. The prothrombin index was slightly reduced at the 1% level. BHT quinone methide was not detected in guinea pigs, whereas 7–40 mg/g liver was detected in rats. In rabbits, dogs, and Japanese quail fed BHT for 14–17 days at levels of 170 or 700 mg/kg bw, 173, 400, or 760 mg/kg bw, and 1%, respectively, no hemorrhages were observed (Table 5.10) (122,126).

A number of studies have shown that BHT causes acute pulmonary toxicity in

Table 5.10 Hemorrhagic Effects of BHT in Various Species

Species and strain	Sex	Dose of BHT	Mean intake of BHT[a] (mg kg^{-1} day^{-1})	% Total population population with hemorrhages		Mean prothrombin index[b] (%)	Hepatic level of quinone methide[c] (μg/g liver)
				Dead	Surviving		
Rat							
Sprague-Dawley	M	0	0 (31)	0	0	101	
		1.2%	693 (50)	44	50	18***	NC
	F	0	0 (5)	0	0	101	
		1.2%	1000 (10)	0	30	73***	NC
Wistar	M	0	0 (5)	0	0	100	
		1.2%	638 (10)	10	90	22***	38
	F	0	0 (5)	0	0	100	
		1.2%	854 (10)	0	100	38***	7
Donryu	M	0	0 (5)	0	0	100	
		1.2%	1120 (10)	10	70	13***	41
	F	0	0 (5)	0	0	100	
		1.2%	1000 (10)	0	0	92	27
Fischer	M	0	0 (5)	0	0	100	
		1.2%	821 (10)	30	70	5***	16
	F	0	0 (5)	0	0	100	
		1.2%	895 (10)	20	70	18***	11
Mouse							
ddY	M	0	0 (5)	0	0	100	
		1.2%	1701 (10)	0	30	79**	ND
ICR	M	0	0 (10)	0	0	100	
		1.2%	1344 (10)	0	0	96	ND
DBA/2	M	0	0 (10)	0	0	100	
		1.2%	847 (10)	0	0	138**	NC

		1.2%	821 (10)	30	70	5***	16
	F	0	0 (5)	0	0	100	
		1.2%	895 (10)	20	70	18***	11
Mouse							
ddY	M	0	0 (5)	0	0	100	
		1.2%	1701 (10)	0	30	79**	ND
ICR	M	0	0 (10)	0	0	100	
		1.2%	1344 (10)	0	0	96	ND
DBA/2	M	0	0 (10)	0	0	100	
		1.2%	847 (10)	0	0	138**	NC
BALB/cAN	M	0	0 (5)	0	0	100	
		1.2%	1730 (10)	0	0	84**	NC
C3H/He	M	0	0 (10)	0	0	100	
		1.2%	1858 (10)	0	0	115***	NC
C57BL/6	M	0	0 (5)	0	0	100	
		1.2%	1925 (10)	0	0	91*	NC
Hamster							
Syrian golden	M	0	0 (5)	0	0	101	
			380 (4)	0	0	101	
			760 (6)	0	0	87	ND[d]
Guinea pig							
Hartley	M	0	0 (5)	0	0	100	
			190 (5)	0	0	78	
			380 (5)	0	0	73	ND[d]
Japanese quail							
White egged	M	0	0 (5)	0	0	100	
		1%	1056 (5)	0	0	53*	ND

[a]The numbers in brackets are the numbers of animals in each group.
[b]The values marked with asterisks differ significantly from the corresponding control values: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. The times of treatment for rats, hamsters, guinea pigs, and quail were 3 weeks, 1 week, 3 days, 3 days, and 17 days, respectively.
[c]NC = Not calculated; ND = Not detected.
[d]Determined in separate experiments in hamsters or guinea pigs at 1.2 or 1% in the diet, respectively, for 3 days.
Source: Ref. 126.

mice at levels of 400–500 mg/kg bw. The effects include hypertrophy, hyperplasia, and a general thickening of the alveolar walls of the lungs. A substantial proliferation of the pulmonary cells accompanied by a dose-dependent increase in total DNA, RNA, and lipids in the lungs was also observed within 3–5 days of a single intraperitoneal (IP) injection of BHT (130–132). The effect was generally reversible in 6–10 days of cessation of the treatment. However, exposure to a second stress such as hyperbaric O_2 after administration of BHT impeded the repair process, resulting in pulmonary fibrosis (133). Some of the morphological and cytodynamic events include perivascular edema and cellular infiltration in type I epithelial cells followed by multifocal necrosis, destruction of the air-blood barrier, and fibrin exudation by day 2 after a single IP injection of 400 mg/kg bw BHT (134). Ultrastructural studies indicated that the type I cells were damaged by day 1 and cell destruction was complete within 2–3 days. Elongation of the type II cells with large nuclei and abundant cytoplasm was evident in 2–7 days (135). It has been postulated that BHT causes cell lysis and death as a result of interaction with the cell membrane (136). However, the mechanism of BHT toxicity still remains unclear.

Long-Term and Carinogenicity Studies. In early studies, Deichmann et al. (113) observed no adverse effects in rats fed 0.2, 0.5, 0.8, or 1% BHT for 2 years. In a 104-week long-term feeding study in rats, Hirose et al. (137) reported that BHT at the 0.25 and 1% levels was not carcinogenic. Treated rats of both sexes showed reduced body weight gain and increased liver weights. Only males showed increased γ-glutamyl transferase levels. Tumors were observed in various organs, but their incidence was not statistically significant compared to controls (Table 5.11). In a two-generation carcinogenicity study with in utero exposure in rats, BHT was fed at levels of 25, 100, or 500 mg/kg bw per day from 7 weeks of age to the weaning of the F_1 generation. The F_1 generation were given 25, 100, or 250 mg/kg bw per day from weaning to 144 weeks of age. At weaning, the BHT-treated F_1 rats, especially the males, had lower body weights than untreated controls. Dose-related increases in the numbers of hepatocellular adenomas and carcinomas were statistically significant in male F_1 rats tested for heterogeneity or analyzed for trend. In F_1 females the increases were statistically significant only for adenomas in the analysis of trend. However, all tumors were detected when the F_1 rats were more than 2 years old (138). Unlike BHA, BHT had no adverse effects on the forestomach of rats or hamsters at the 1% level (76,77).

Carcinogenicity studies have been conducted in various strains of mice. In a 2-year study in B6C3F1 mice, Shirai et al. (139) reported that BHT at the level of 0.02, 0.1, 0.5% was not carcinogenic. A reduction in body weight gain was noticed, the effect being more pronounced in males. Nonneoplastic lesions related to BHT treatment were lymphatic infiltration of the lung in females and of the urinary bladder in both sexes at the highest dose level. Tumors were observed in various

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Table 5.11 Tumor Incidence in Rats Fed BHT

Site and type of tumor	No. of animals with tumors[a]					
	Males			Females		
Treatment group:	Control	0.25%	1%	Control	0.25%	1%
No. of rats[b]:	26	43	38	32	46	51
Liver						
Hyperplastic nodule	2 (7.7)	2 (4.7)	1 (2.6)	0	3 (6.5)	3 (5.9)
Pancreas						
Carcinoma	0	0	1 (2.6)	0	1 (2.2)	4 (7.8)
Islet-cell adenoma	0	1 (2.3)	2 (5.3)	0	0	0
Mammary gland						
Fibroadenoma	—	—	—	6 (18.8)	8 (17.4)	8 (15.7)
Adenoma	—	—	—	1 (3.4)	1 (2.2)	1 (2.0)
Uterus						
Leiomyoma	—	—	—	1 (3.4)	1 (2.2)	0
Carcinoma	—	—	—	1 (3.1)	2 (4.3)	1 (2.0)
Pituitary gland						
Adenoma	2 (7.7)	3 (7.0)	1 (2.6)	0	6 (13.0)[c]	3 (11.8)
Carcinoma	0	2 (4.7)	5 (13.2)	3 (9.4)	3 (6.5)	7 (13.7)
Adrenal gland						
Adenoma	1 (3.8)	3 (7.0)	0	0	2 (4.3)	1 (2.0)
Carcinoma	0		0	0	0	1 (2.0)
Others	2 (7.7)	2 (4.7)	4 (10.5)	2 (6.3)	4 (8.7)	3 (11.8)
Total	6 (23.1)	13 (30.2)	10 (26.3)	11 (34.4)	25 (54.3)	25 (49.0)

[a]Percent of group given in parentheses.
[b]Animals that survived more than 69 weeks were included.
[c]Differs significantly (chi-square test) from the corresponding control value ($P < 0.05$).
Source: Ref. 137.

organs, with a high incidence in the lung, liver, and the lymph nodes. But the incidence was not statistically significant. In another study in the same strain at higher dose levels of 1 or 2% in the diet, a significant dose-dependent increase in hepatocellular adenomas and foci of alterations in the liver were observed in males but not in females (140). Clapp et al. (141) reported an increase in the incidence of lung tumors and hepatic cysts in BALB/c mice fed 0.75% BHT for 16 months. Brooks et al. (142) reported a dose-related increase in both benign and malignant tumors in the lung in both sexes of CF1 mice and benign ovarian tumors in females. In C3H mice, which are more likely to develop spontaneous liver tumors with age, BHT fed at levels of 0.05 or 0.5% for 10 months increased the incidence of liver tumors in males, but it was not dose-related. The incidence of lung tumors was increased in males at both dietary levels but in females only at the higher dose level (143).

A number of studies have been conducted on the modifying effects of BHT on chemical carcinogenesis. These effects depend on a number of factors including target organs, type of carcinogen, species and strain differences, type of diet used, and time of administration. In general, BHT inhibited the induction of neoplasms in the lung and forestomach in mice and neoplasms in the lung, liver, and forestomach in rats when given before or with the carcinogen. BHT had a promoting effect on urinary bladder, thyroid, and lung carcinogenesis (144).

Reproduction. In an earlier study, Brown et al. (69) reported that rats fed 0.1 or 0.5% BHT showed a 10% incidence of anophthalmia. These findings were not confirmed in any other laboratory. BHT had no adverse effects on reproduction data and was not teratogenic in single or multigeneration reproduction studies in rats, mice, hamsters, rabbits, and monkeys at lower doses, and the no-effect level was equivalent to 50 mg/kg bw (84,88,145–149). At higher dose levels, some of the significant effects observed in rats include a dose-related response in litter size, number of males per litter, and body weight gain during lactation, but the effects were significant only at 500 mg/kg bw per day. In rabbits given 3–320 mg/kg bw per day by gavage during embryogenesis, an increase in intrauterine deaths was observed at high doses. In mice at 500 mg/kg bw per day, prolonged time to birth of first litters and a reduction in pup numbers and pup weight were observed.

In a developmental neurobehavioral toxicity test, the offspring of rats fed 0.5% BHT before conception and throughout pregnancy and lactation showed delayed eyelid opening, surface righting development, and limb coordination in swimming in males and reduced female open-field ambulation. However, the results did not suggest any specific toxicity of BHT for the central nervous system (150). In another study weanling mice fed 0.5% BHT for 3 weeks, whose parents had been maintained at the same level during their entire mating, gestation, and preweaning period, decreased sleeping, increased social and isolation-induced aggression, and learning disabilities were observed under the experimental conditions employed (89).

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Mutagenicity. Butylated hydroxytoluene was found to be negative in several strains of *Salmonella typhimurium* with or without metabolic activation (151,152). In in vitro tests using mammalian cells, BHT was weakly positive in the test for gene mutation in Chinese hamster V79 cells (153). BHT was positive in tests for chromosomal aberrations in human lymphocyte cultures (154) and in Chinese hamster ovary cells (155). In in vivo tests, BHT was negative in tests for chromosomal damage in bone marrrow cells and liver cells of rats (156,157). In mice, BHT was negative in three dominant lethal tests, but in rats at high doses BHT was positive in two dominant lethal tests (158,159). In general, the mutagenic effects were observed only at higher levels of BHT.

tert-*Butyl Hydroquinone*

tert-Butyl hydroquinone (TBHQ) was introducted in the 1970s and was approved as a food grade antioxidant in 1972. TBHQ is used for the stabilization of fats and oils, confectionery products, and fried foods and is regarded as the best antioxidant for the protection of frying oils and the fried product (160). TBHQ is currently being used in the United States and some other countries but is not permitted for food use in the EEC countries and Japan (161,162) due to lack of adequate toxicological data. In the 1987 reevaluation, JECFA allocated a temporary ADI of 0–0.2 mg/kg bw (1).

TOXICOLOGICAL STUDIES

Absorption, Metabolism, and Excretion. Absorption and metabolism studies have been conducted in rats, dogs, and humans. In all three species, more than 90% of an orally administered dose of TBHQ was rapidly absorbed and nearly 80% was excreted in the urine in the first 24 h. The excretion was essentially complete within 48 h. In rats given single oral doses of TBHQ (100 mg/kg), about 57–80% was excreted as the 4-*O*-sulfate, 4% as the 4-*O*-glucuronide conjugate, and about 4–12% of unchanged TBHQ was observed (Fig. 5.7). In long-term studies, an increase in the amount of glucuronide was observed. A similar pattern was observed in dogs, but the proportion of glucuronide was higher. No tissue accumulation of TBHQ was observed. In humans given single oral doses of 0.5–4 mg/kg in a high-fat vehicle, most of the dose was recovered within 40 h in the urine. The proportions of the major metabolites observed were 73–88% of 4-*O*-sulfate, 15–22% of 4-*O*-glucuronide, and less than 1% unchanged TBHQ. In a low-fat vehicle, absorption was much lower, and urinary elimination accounted for less than half the intake (Table 5.12) (163).

Acute Toxicity. The acute oral and intraperitoneal LD_{50} in mg/kg bw in rats was 700–1000 and 300–400, respectively. In mice, the acute oral LD_{50} was 1260 mg/kg bw, and in guinea pigs it was 790 mg/kg bw (163,164).

X. Related Proceedings Appendix

None.